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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1956

ORIGINAL ARTICLES

REQUIREMENTS FOR PERSISTENT IMMUNITY TO POLIOMYELITIS*†

By Jonas E. Salk, M.D.

(From the Virus Research Laboratory, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania)

The demonstration that resistance to paralysis (Francis *et al.*[3] and Langmuir, Nathanson and Hall[5]) can be induced by the use of a noninfectious poliomyelitis virus vaccine (Salk[9]) has brought to the fore questions as to the duration of such immunity. Before discussing this specifically, it would be of interest to inquire more generally into the mechanism and hence the requirements for persistent immunity to this disease.

NATURALLY ACQUIRED IMMUNITY. From observations under natural circumstances, it would appear that infection results in life-long immunity (Paul and Riordan[8]). The development of this state of resistance is accompanied by the appearance of antibody in the circulating blood. From knowledge of the pathogenesis of paralytic disease, the role of antibody in the serum in intercepting central nervous system invasion is clear (Bodian[1]). However, there are individuals in whom serum antibody is not demonstrable; that such individuals had had previous contact with the antigens concerned, is readily shown, after an injection of vaccine, by the rapid outpouring of large quantities of antibody into the circulating blood. That such persons are resistant to paralysis is suggested by a number of observations. The question then is, by what mechanism is the state of immunity maintained in such individuals (Salk[10]).

THE ROLE OF INCUBATION PERIOD FOR THE MAINTENANCE OF IMMUNITY. From the studies on pathogenesis of the disease in man and in chimpanzees, Bodian[2] has suggested (Fig. 1) that the infectious process is divided, in general, into four phases, with approximately 7 days for the incubation period preceding onset of systemic symptoms, and approximately 5 days for the systemic component that precedes the onset of neural symptoms. It is as if the total incubation period before appearance of symptoms of central nervous system infection is approximately 12 days.

In his discussion of the question of the role of the length of the incubation

*Studies referred to aided by a grant from The National Foundation for Infantile Paralysis.

†Presented before 69th Annual Meeting of the Association of American Physicians, Atlantic City, New Jersey, 1 May 1956.

period in contributing to life-long immunity, MacLeod[6] has pointed up the essential part played by primary sensitization of the immunologic mechanism together with length of incubation period. Figure 2, taken from MacLeod's paper that deals with a general phenomenon in immunology and not with poliomyelitis specifically, indicates that the speed with which renewed antibody formation begins in the immunologically experienced individual is such as to provide a reasonable explanation for the existence of a state of immunity even in the absence of a demonstrable level of circulating antibody.

The way in which this phenomenon might operate in poliomyelitis specifically is shown in Fig. 3 (Salk[10]). This

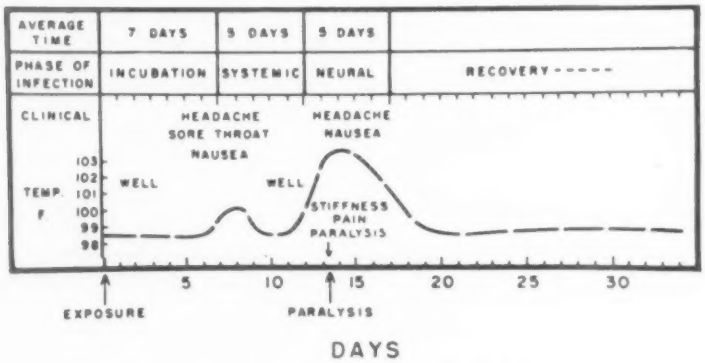

Fig. 1.—Diagram showing time relations of clinical and pathogenic events in paralytic poliomyelitis infections. Many of the data on which the illustration is based come from studies of the human disease, but quantitative details are supported by experimental studies in other primates. (D. Bodian, 3rd Inter. Polio. Conf., 1954.)

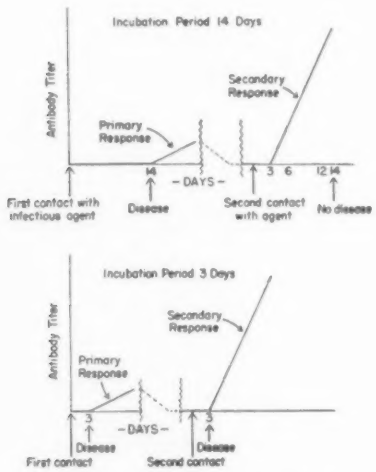

Fig. 2.—Graphic representation of the relationship of the secondary antibody response and the incubation period to permanent immunity (C. M. MacLeod, J. Imm., 1953.)

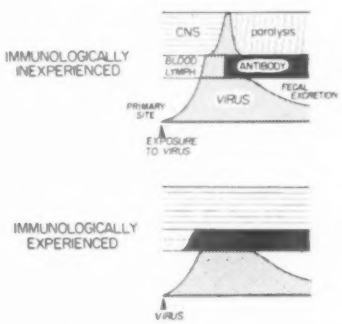

Fig. 3.—Concept of influence of previous immunologic experience in the prevention of paralysis.

chart, drawn schematically, illustrates the early presence of virus in the intestinal tract; indicating the primary source of antigenic stimulation. It illustrates, also, the common observation that antibody is demonstrable in the circulating blood at the time of onset of paralysis. It is this fact that is responsible for the termination of the viremia before the end of the systemic phase; thus, the earliest appearance of antibody resulting from first contact with virus often occurs too late to prevent central nervous system invasion. If the rate of development and time of appearance of antibody is accelerated, as in the case of the immunologically experienced individual, then immunity to paralysis, in poliomyelitis, could exist merely by virtue of the existence of a hyper-reactive state. The hyper-reactive state could furnish antibody sufficiently early, after a later contact with virus, to prevent neural infection, even if level of antibody at the time of exposure is insufficient in concentration to prevent establishment of the systemic infection.

ACCELERATION AND POTENTIATION OF ANTIBODY FORMATION RESULTING FROM PRIOR ANTIGENIC EXPERIENCE. The speed with which antibody appears after vaccination in previously sensitized persons is shown in Figs. 4 and 5. As is shown here, the injection of antigen causes antibody to begin to rise sometime between the third and fourth day. Thus, it would seem that a relatively wide margin exists between this point in time and the expected end of the incubation period. The acceleration and exaggeration of antibody formation provides one component of the complex whereby paralysis may be prevented, the total complex requiring that a sufficient margin exist between the time of appearance of antibody and the end of the incubation period before onset of symptoms of disease.

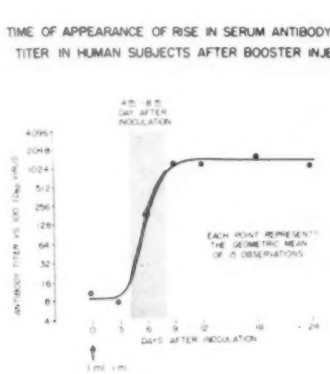
TIME OF APPEARANCE OF RISE IN SERUM ANTIBODY TITER IN HUMAN SUBJECTS AFTER BOOSTER INJECTION
EACH POINT REPRESENTS THE GEOMETRIC MEAN OF 15 OBSERVATIONS
DAYS AFTER INOCULATION

Fig. 4

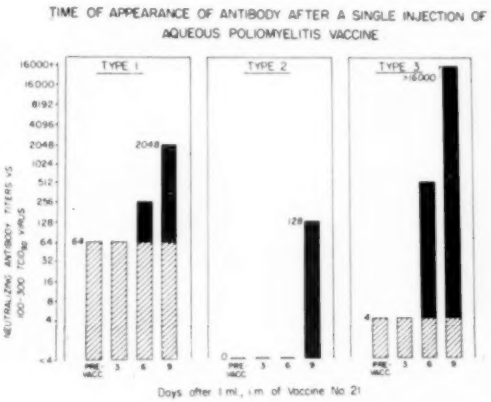
TIME OF APPEARANCE OF ANTIBODY AFTER A SINGLE INJECTION OF AQUEOUS POLIOMYELITIS VACCINE
TYPE 1
TYPE 2
TYPE 3
Days after 1 ml. i.m. of Vaccine No 21

Fig. 5

Although this reasoning may be very plausible, it does not answer the question: has this phenomenon been demonstrated to be operative in the prevention of disease under natural circumstances? This can now be answered in the affirmative since we have reaffirmed our observation (Salk[10]) of a naturally occurring phenomenon illustrating that the *minimum requirement* for immunity to paralytic poliomyelitis

is the existence of an immunologically hyper-reactive state, and not necessariy one accompanied by a demonstrable level of antibody. These observations were made quite incidentally while in search for answers to other questions.

IMMUNOLOGIC COMPLEXITY. The first pertinent observation is that individuals differ from one another in their response to vaccination, depending upon their prior immunologic experience. For example, individuals who, prior to vaccination, have no demonstrable type I antibody, do not all respond alike. The character of the response depends upon whether or not they possess antibody for types II or III virus, or are devoid of naturally acquired antibody for any of the three types. By and large, as is shown in Fig. 6, individuals who have had a prior type II infection, as evidenced by the presence in their serum only of type II antibody, react more sharply to the type I component of the vaccine than do individuals who have had a prior type II infection; individuals who have had no prior experience with any of the poliomyelitis viruses are the least reactive of all. Persons with antibody for both types II and III react as do those with either type II or III alone. The possible reason for this will be reported upon and discussed elsewhere.

It would appear from these observations that the type I viruses that have been in circulation in recent years, possess, for the most part, but probably not in all instances, a meaningful quantity of type I antigen. It seems

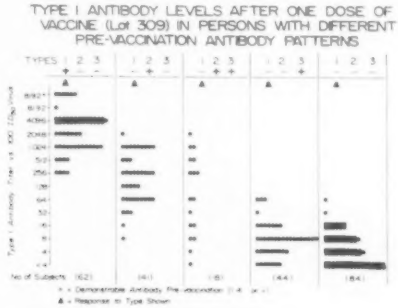

Fig. 6

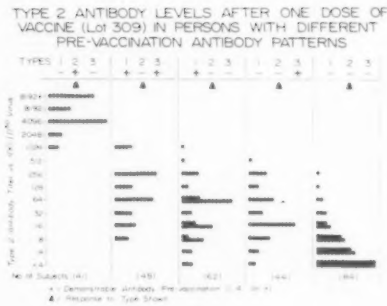

Fig. 7

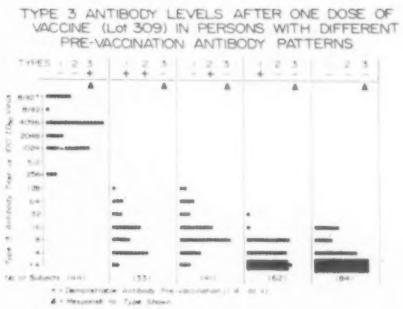

Fig. 8

equally clear that the type III viruses that have been in circulation in recent years possess little, if any, configurations characteristic of type I antigenic material.

Similar analyses (Figs. 7 and 8) reveal that type I viruses in circulation in recent years possess antigenic components that are characteristic of type II viruses; this appears to be true to a lesser degree than the extent to which type II virus possesses type I antigen. The types I and III viruses appear, for the most part, to be free of shared antigens that cross-react with each other. On the other hand, type II viruses cross with type III, almost to the same extent that they cross with type I. These relations are summaried diagrammatically in Fig. 9.

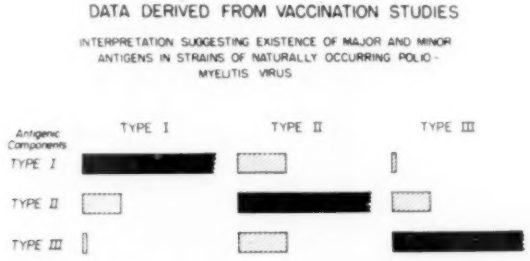

Fig. 9

The existence of antigenic configurations for more than one type, among different strains of poliomyelitis virus, has been observed and demonstrated in a variety of ways by others. For example, Melnick[7] has reported the extent to which, by complement-fixation, he found evidence for type II antigenic material in a number of type I and type III viruses; however, with but minor exceptions, strains of types I and III were totally unrelated antigenically.

IMMUNITY IN THE ABSENCE OF DEMONSTRABLE CIRCULATING ANTIBODY. Another observation that bears on the question under consideration comes from studies on the relative frequency with which each of the three virus types cause nonparalytic as well as paralytic infections. Data shown in Fig. 10 indicate that antibody for each of the three virus types tends to appear in a large population group at more or less the same rate, although there are evident differences. The rate at which each virus causes infection through a population over a period of years is reflected by the rate of increase of individuals who have acquired antibody. In the groups in which these studies were conducted the type I virus seems to have circulated more actively, since it seems to have induced more infections; type III next, and type II least. It has been shown by many that the type I virus, as a cause of the paralytic disease, occurs approximately six to eight times more frequently than types II or III. Additional data in support of this are contained in Fig. 11. Thus, the type I virus is clearly far more active than types II and III as a cause of paralysis. The striking disproportion between the relative frequency of occurrence of *infection* with each of the three virus types, and the relative frequency of *paralysis* due to each type, indicate (Fig. 11) not only that the type I virus has been

more paralytogenic than the types II or III, but that the type III virus, in general, has been the least pathogenic.

It is worthy of note that the frequency with which virus of a given type induced paralysis can be revealed not only by studies on virus isolations, but by serologic studies in paralyzed individuals who possess antibody for another type. This is evident from the frequency with which combinations of antibody for any two types occur as compared with the frequency with which antibody for but one type tends to occur (Fig. 12). Nonparalytic infections with types I and II, or I and III, or II and III, seem to occur at a frequency such as to suggest that each of

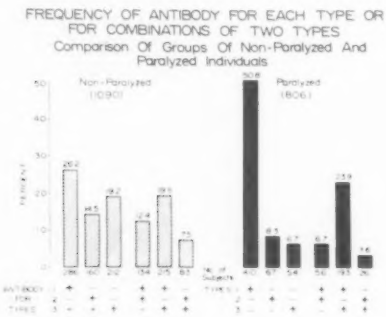
FREQUENCY OF ANTIBODY FOR EACH TYPE OR FOR COMBINATIONS OF TWO TYPES
Comparison Of Groups Of Non-Paralyzed And Paralyzed Individuals
Non-Paralyzed (1090)
Paralyzed (806)
PERCENT
ANTIBODY FOR TYPE
No. of Subjects
TYPES

Fig. 10

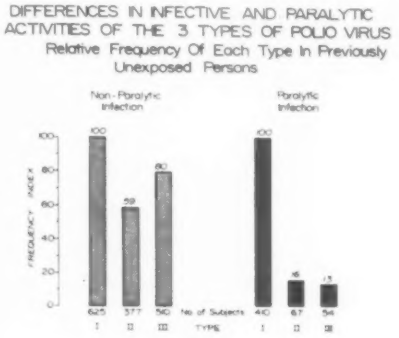
DIFFERENCES IN INFECTIVE AND PARALYTIC ACTIVITIES OF THE 3 TYPES OF POLIO VIRUS
Relative Frequency Of Each Type In Previously Unexposed Persons
Non-Paralytic Infection
Paralytic Infection
FREQUENCY INDEX
No of Subjects
TYPE

Fig. 11

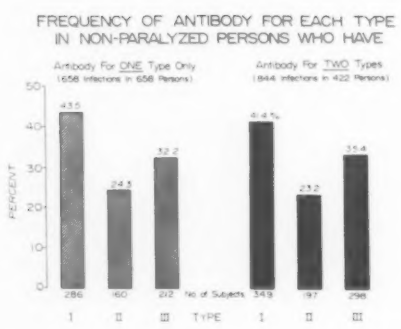
FREQUENCY OF ANTIBODY FOR EACH TYPE IN NON-PARALYZED PERSONS WHO HAVE
Antibody For ONE Type Only (658 Infections in 658 Persons)
Antibody For TWO Types (844 Infections in 422 Persons)
PERCENT
No of Subjects
TYPE

Fig. 12

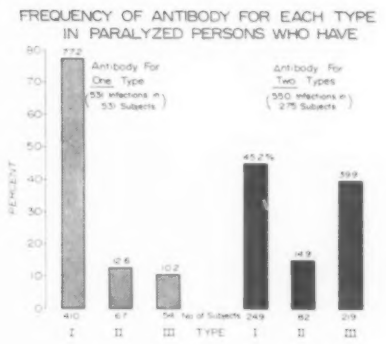
FREQUENCY OF ANTIBODY FOR EACH TYPE IN PARALYZED PERSONS WHO HAVE
Antibody For One Type (531 Infections in 531 Subjects)
Antibody For Two Types (550 Infections in 275 Subjects)
PERCENT
No of Subjects
TYPE

Fig. 13

one type only. Data on frequency of nonparalytic infection can be derived more readily from serologic studies than from attempts at virus isolation.

In an extension of these studies, it has been observed that the occurrence of prior infection with virus of one type seems not to interfere with the acquisition of infection by virus of the two infections is acquired apparently without influence of the existence of the one first acquired. Thus, it would appear that there is no evidence from these data of any substantial cross immunity to infection *per se*.

If, however, one examines a group of paralyzed individuals, the relationships appear to be quite different (Fig. 13).

Data in Fig. 14 suggest that a previous type II infection will reduce the likelihood of developing type I paralysis whereas a previous type III infection does not have a similar effect. It is clear from Fig. 14 that the frequency with which combinations of antibody for types I and II were found, in groups of paralyzed individuals, was far less than the frequency with which combinations of antibody for types I and III occurred; also, combinations of antibody for types II and III were less than

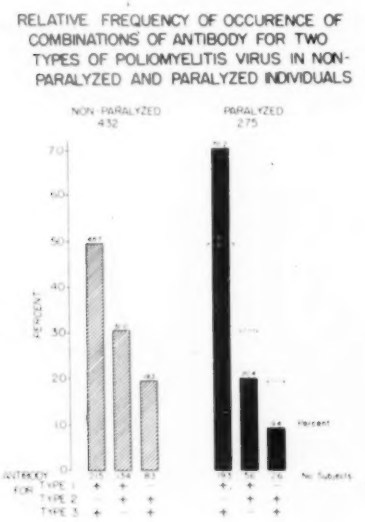

Fig. 14

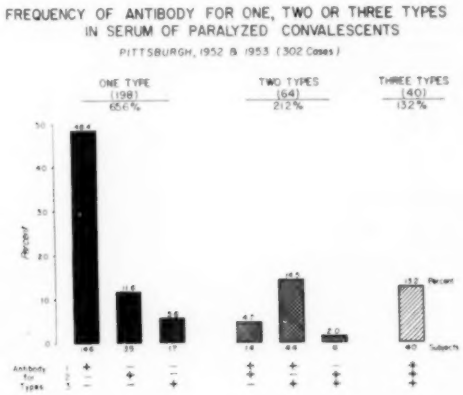

Fig. 15

expected as compared with the frequency of occurrence of combinations of types I and III.

Since type I virus is the most paralytogenic (Fig. 15), it is not unreasonable to assume that the type I virus was, for the most part, responsible for the paralyzing infection in persons with antibody for types I and II or I and III. It appears, therefore, that whether or not type I paralysis occurred was influenced by whether or not the individual had had a prior type II or type III infection. The indications are (Figs. 14 and 15) that a prior type II infection, in some individuals at least, confers a substantial measure of immunity to the development of type I paralysis. A prior type III infection, if it confers any such benefit at all, does so to a far lesser degree than does the type II infection.

A reasonable explanation for this is found in the observation to which reference was made earlier, that type II infections often induce a state of hyper-reactivity not only to type II virus (Fig. 7) but to type I as well (Fig. 6), whereas a type III infection seems not to induce any measurable degree of type I hyper-reactivity. It would appear, therefore, that type I paralysis is, at times, prevented even in the absence of demonstrable circulating antibody if the antibody responding mechanism is hyper-reactive to a sufficient degree; the degree of hyper-reactivity resulting from exposure to the type I antigen that is contained in some, if not most type II virus strains, seems to be sufficient, at least in some individuals.

Horstmann[4] has referred to an observation, by Sabin, in cynomolgus

monkeys which possessed type II antibodies either as a result of inapparent infection after ingestion of the Y–SK strain, or as a result of vaccination with formalin-killed Y–SK tissue culture virus. Sabin and his associates had observed that there was considerably *less paralysis* on oral challenge with the type I Mahoney strain than occurred in control animals which had never been exposed to type II Y–SK virus. Horstmann calls attention to the significance of Sabin's point that none of the animals with Y–SK antibodies was protected against *infection* with type I virus, for all developed antibodies, but there was some protection against *paralysis*, that is, the infection was modified and was milder.

Horstmann taking cognizance of the clinical and epidemiologic features of poliomyelitis, observed that ". . . it seems not unlikely that, in the human population, the vulnerability of the young child, as far as paralysis is concerned, might be due to the larger number for whom the clinical attack, as a result of a virulent epidemic strain, represents the first infection *with any type*. Correspondingly, the higher incidence of nonparalytic cases in older children in epidemics might be correlated with the possession of heterologous antibodies which modify the clinical response."

The observations referred to in the early portion of this section suggest that the "heterologous antibodies" are probably contributed through the effects of heterologous immunologic hyper-reactivity.

Summary. It would seem reasonable to conclude, therefore, that a state of immunologic hyper-reactivity induced by a type II infection is sufficient in some individuals to prevent the later development of type I paralytic poliomyelitis even though, at the time of exposure to the type I virus, there is no demonstrable type I antibody in the serum.

Although a state of immunologic hyper-reactivity may be induced by minimal antigenic stimulation, such a state is induced more forcibly and with greater certainty by a strong antigenic stimulation. It would seem not unreasonable to conclude that once a good and substantial antigenic stimulus has been induced *by any means* that durable immunity has also been induced. The question of duration of persistence of antibody in the blood following vaccination may merely be of academic interest since, in the presence of a sufficiently hyper-reactive state, immunity to paralysis may well continue even after the level of circulating antibody declines to minimal or nonmeasurable levels. Under such circumstances, the question of the reversion of a population of *immune children* into a population of *susceptible adults* seems unlikely. The indications thus far are that hyper-reactivity after vaccination tends to persist (Salk[11]); the longest test-interval that has been possible thus far has been 3 years.

Since the qualitative and quantitative factors that are of importance for inducing the hyper-reactive state or for inducing good levels of antibody are understood, the question of the clinical and epidemiological significance of immunity, based upon hyper-reactivity in the absence of circulating antibody, while it is of considerable theoretical significance, it may be of less practical importance in view of the ease with which good levels of antibody can be induced and are maintained.

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SUMMARIO IN INTERLINGUA

Requirimentos de Persistente Immunitate a Poliomyelitis

Le datos presentate permitte le conclusion que un stato de hyperreactivitate inducite per un infection del typo II suffice in certe individuos pro prevenir le subsequente disveloppamento de paralytic poliomyelitis del typo I, ben que al tempore del exposition al virus del typo I il ha nulle demonstrabile anticorpore al typo I in le sero.

Ben que un stato de hyperreactivitate immunologic pote esser inducite per un minimo de stimulation antigenic, ille stato es inducite plus vigorose- e assecuratemente per un forte stimulation antigenic. Il pare permittite concluder que le induction de un bon e forte stimulo antigenic per *non importa qual medio* significa le induction simultanee de un immunitate durabile. Il es possibile que le question del duration del persistentia de anticorpore in le sanguine post le vaccination es un question de interesse purmente academic, viste le factor que in le presentia de un stato sufficientemente hyperreactive immunitate a paralyse pare continuar, mesmo post que le nivello de anticorpore circulante ha descendite a valores minimal o non mesurabile. Sub tal conditiones, le risco del reversion de un population de *juveniles immun* in un population de *adultos susceptibile* non pare esser multo real. Le datos nunc disponibile indica que hyperreactivitate post vaccination tende a persister (Salk[11]). Le plus extense intervallo de observation usque nunc obtenite es un intervallo de 3 annos.

Proque le factores qualitative e quantitative que importa in le induction del stato hyperreactive o in le induction de bon nivellos de anticorpore es comprendite, le question del signification clinic e epidemiologic de immunitate super le base de hyperreactivitate in le absentia de anticorpore circulante, ben que de considerabile interesse theoric, ha forsan un restringite importantia practic in consequentia del facto que bon nivellos de anticorpore es facile a inducer e facile a mantener.

IMMUNIZATION OF CHILDREN BY THE FEEDING OF LIVING ATTENUATED TYPE I AND TYPE II POLIOMYELITIS VIRUS AND THE INTRAMUSCULAR INJECTION OF IMMUNE SERUM GLOBULIN

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In a series of previous reports[2,3,4,5], evidence was presented which indicated that the oral administration of attenuated living poliomyelitis virus (Types I and II) to nonimmune children produced a significant rise in blood antibodies against the types of virus fed. Clinical signs of infection were always absent. In this presentation, similar results of a new trial with simultaneous administration of the attenuated viruses and immune serum globulin will be reported. Finally, attempts to control the prolonged excretion of virus in the stools by the use of calomel will be discussed.

Methods and Material. STRAINS OF VIRUS. Two attenuated strains of virus were used in the present trial; the TN[4] representing Type II and the SM[6] strain representing Type I. The TN strain, a rodent-adapted Type II virus, was prepared as mouse brain and cord suspension representing the 18th passage of the virus in PRI mice. It was noncytopathogenic for tissue culture-grown fibroblasts or epithelium of either simian or human (normal and neoplastic) origin[2], and its presence had to be determined through the intraspinal inoculation of adult Swiss albino mice.

The SM strain, also rodent-adapted, can be maintained, with the help of alternating passages through cultures of monkey kidney, in chick embryo tissue cultures. This strain is cytopathogenic for monkey kidney epithelium, and its presence was determined either by observation of cytopathic changes in tissue culture tubes or by counting virus plaques on monolayers of epithelium derived from monkey kidney (Dulbecco and Vogt[1]).

The virus was always given by the oral route, either mixed with from 10 to 20 ml. of milk or in capsule form. To prepare the capsules, virus-containing material was thawed from the frozen state and, either undiluted or diluted to the desired concentration in balanced salt solutions, was mixed in equal proportion with polyethylene glycol 400. The mixture was placed in hard gelatin capsules in 0.5-ml. amounts. The outside of each capsule was then rinsed thoroughly in running tap water.

SUBJECTS OF THE TRIAL. Physically healthy inmates of an institution for mental defectives were chosen as subjects for the trial after permission was secured from the parents of each child. Prior to the start of the trial the

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individuals were bled and the antibodies against poliomyelitis in their blood determined by tissue culture neutralization tests. Twenty children from 6 to 12 years old lacking antibodies to the type of virus to be administered were chosen. (See Table 1.)

Immediately after they were fed the virus, the children were kept in two quarantined areas and strict isolation techniques were enforced. One area contained those children who were fed Type I alone, while the other contained those subjects who received both Type I and Type II viruses. Individuals were not released from isolation until three successive stool examinations were found to be negative for the presence of poliomyelitis virus.

The children were divided into three groups: the first group (AA) 6 in number, comprised individuals who had no neutralizing antibodies against either Type I or Type II poliomyelitis virus. In addition, 2 of the 6 had no antibodies against Type III virus. The second group (BB) was composed of 8 children who were found to have no neutralizing antibodies against Type I virus; 6 of this group had no Type II antibodies although 7 did have antibodies against Type III. The remaining 6 children (group CC) had no antibodies against Type I but 5 of them possessed antibodies against Types II and III, while one had Type II antibodies only.

ADMINISTRATION OF IMMUNE GLOBULIN. Human immune serum globulin, 0.15 ml. per pound of body weight (but not more than 10 ml.), was given intramuscularly at the time of virus feeding.

TABLE 1.—SUMMARY OF VIRUS FEEDING

Clinical Trial Group	*Subject No.*	*Pre-immunization Status: Presence of Antibodies*	*Virus Fed*			
			Type	*Amount PD_{50} or TD_{50}*	*Remarks*	
AA	1	III	I + II	3.2 + 6.6	S, L	
	2	None				
	3	III				
	4	III				
	5	None				
	6	III				
BB	13	None	I + II	2.8 + 5.0	P, L	t
	14	III	I + II	2.8 + 5.0	P, L	t
	15	III	I + II	2.6 + 5.0	P, cs	t
	16	III	I + II	2.6 + 5.0	S, cs, cal	t
	17	III	I + II	3.1 + 5.0	S, L, cal	t
	18	III	I + II	3.1 + 5.0	S, L	t
	19	II, III	I	4.9	L*, cal	t
	20	II, III	I	4.7	cs*, cal	t
CC	27	II, III	I	4.8	cs*, cal	
	28	II, III				
	29	II, III				
	30	II, III				
	31	II, III				
	32	II				

Type I = SM strain
Type II = TN strain
S = Simultaneous administration of both viruses
P = Type II administered 5 days before Type I
t = Throat swabs collected
L = Both viruses administered in milk
cs = Type I administered in capsule; Type II administered in milk
cs* = Type I only (in capsule)
cal = Calomel treated
L* = Type I only (in milk)

COLLECTION OF STOOLS. Stool specimens were collected daily from every subject of the trial. An 8- to 12-gm. sample of each stool was then placed in a plastic centrifuge tube which was kept at a temperature below −20° C. Twice a week the tubes were put in a shaking machine for a period of 18 hours at +4° C. Equal amounts of suspensions representing specimens collected from the same individual over a 4-day period were pooled. The pool was centrifuged under refrigeration for 60 minutes at 11,000 rpm. The supernatant was filtered through a small paper

filter and enough penicillin and streptomycin were added to the filtrate to equal a concentration of 1,000 units of penicillin and 20 mg. of streptomycin per ml. The supernatant was then used either for inoculation of mice and tissue culture tubes or, if toxic to tissue, was submitted to another cycle of centrifugation at 14,000 rpm for 60 minutes before being used. If no cytopathogenic effect was observed, 3 blind passages in tissue culture were made before the specimen was considered negative.

COLLECTION OF PHARYNGEAL SECRETIONS. Throats of the subjects in one group were swabbed daily for 10 days following the feeding of the virus. The swabs were placed in 1 ml. of balanced salt solutions, the material expressed into the fluid, and then each sample was inoculated into 6 monkey kidney tubes for the determination of Type I virus. If no cytopathogenic effect was observed, three blind passages were made in tissue culture before the specimen was considered negative.

ADMINISTRATION OF CALOMEL. Since organic and inorganic mercurials are known to be effective in controlling virus-induced alimentary infection of mice due to encephalomyelitis (TO) virus, calomel was given to one group of subjects in an attempt to suppress viral excretion. In this trial, calomel was administered orally at a dosage of 0.0065 gm. every half hour for four doses, twice daily, to a total of 0.05 gm. per day. The duration of medication varied and is stated in the respective protocols.

NEUTRALIZATION TESTS. The tissue culture neutralization test technique described by Youngner, Salk and Ward[10] was adopted, using serial fourfold dilutions of antiserum mixed with 100–1,000 TCD_{50} of the respective virus type. In several cases, results were checked by a roller tube test in which the presence of cytopathic lesions was observed directly under the microscope[4] instead of through the observation of pH changes. The latter procedure was used for the identification of viruses isolated from the feces of all subjects.

Results. Information on the serological status of the patients prior to virus administration, the types of virus fed, the dosage and the form in which the virus was administered, are summarized in Table 1.

Group AA was fed 3.2 TD_{50} of Type I and 6.6 PD_{50} of Type II virus simultaneously in milk. Group BB also received the two types of virus, either simultaneously or at 5-day intervals, in milk or in capsule form, as indicated in Table 1. Two subjects of this group received Type I virus only, since, as previously noted, they already had antibodies against Type II. Throat swabs were collected from all subjects in this BB group. Group CC was fed 4.8 TD_{50} of Type I virus in capsule form.

EXCRETION OF VIRUS IN STOOLS. Type II virus was not excreted by the 12 individuals who received it in conjunction with Type I. Conversely, Type I virus was recovered from stools of all the subjects. The duration of excretion and the titer of the excreted virus are shown in Table 2. From this table it may be seen that, even disregarding individuals who were treated with calomel (see below), the excretion of Type I virus in stools did not conform to any established pattern. For instance, subjects Nos. 13 and 14 stopped excreting virus on the 24th day after its administration, whereas subject No. 18, who received the same amount of virus, was found to excrete the virus for 164 days. The highest concentrations of excreted virus were observed in stools collected between the 1st and 15th days after virus administration. There were, however, exceptions to this rule. For instance, the virus titers exceeded $10^{5.5}$ per gm. of fecal material in the stool of subject No. 17 collected between the 83rd and 102nd days of the trial.

ANTIBODY RESPONSE. As shown in Fig. 1, all 6 children in group AA developed a significant rise in neutralizing antibodies to Type I virus. Two of the 6 children failed to develop Type II antibodies and in one child the titer was low. This was caused by the interference phenomenon to be discussed more fully below, and which had been observed previously when "mixed" feeding of the two types took place.

TABLE 2.—CONCENTRATION OF TYPE 1 VIRUS IN STOOLS OF HUMAN SUBJECTS FED THE SM STRAIN OF POLIOMYELITIS

Stools Collected and Pooled Days after Virus	*TD_{50} Titer per gm. of Fecal Material Obtained from Subjects*																			
	1	*2*	*3*	*4*	*5*	*6*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*27†*	*28†*	*29†*	*30†*	*31†*	*32†*
1–3	4.2	5.9	..	5.0	6.5	5.2	6.2	5.7	5.5	5.2	5.5	6.5	4.7	5.7	4.5	4.8	5.7	4.7	Neg	4.5
8–11	5.2	6.0	6.2	4.5	6.2	6.0	6.5	..	..	5.7	..	..	*Neg	*Neg	*3.5	*5.5	*4.5	*3.2	*4.5	*3.2
															3.2	5.2	4.7	Bl.	5.2	
12–14	4.7	5.2	5.5	4.7	5.5	5.2	5.5	4.5	4.7	4.7	5.7	5.5	*Neg	*Neg	Neg	4.2	Neg	**Neg	Bl.	4.0
15–17	4.5	4.5	5.2	3.5	4.5	5.2	..	4.7	4.5	..	..	..	*Neg	*Neg	**Neg	**4.5	**Neg	Neg	**Neg	**4.2
18–20	..	4.0	5.7	3.7	5.2	4.5	5.7	..	..	5.5	5.2	5.2	..	..	..	4.5	..	..	..	..
21–24	5.5	5.2	5.7	4.2	4.5	5.2	3.7	Bl.	Neg	Bl.	Bl.	Bl.	**Neg	**Neg	4.5	4.5	Neg	Neg	Neg	Neg
25–28	4.5	Bl.	5.5	4.7	4.2	4.7	Neg	..	*Neg	*Neg	*Neg	Neg	Neg	Neg	Neg	4.7	..	..	Neg	Neg
33–36	4.5	Bl.	..	..	Bl.	Bl.	Neg	Neg	Neg	*4.7	*4.5	3.7	Neg	Neg	Neg	Neg	..	..	..	..
45–48	Bl.	Bl.	Bl.	Bl.	Bl.	Neg	..	..	..	**4.0	**3.5	3.5	..	..	..	3.2	..	..	..	..
64–68	Neg	4.5	Neg	Neg	..	Neg	..	..	..	Neg	4.7	4.5	..	..	..	Neg	..	..	..	..
69–82	..	Neg	..	..	..	Neg	..	..	..	Neg	>5.5	3.7	..	..	..	..	..	..	..	..
83–92	..	..	..	..	..	..	..	..	..	..	>5.5	Bl.								
93–102	..	..	..	..	..	..	..	..	..	..	>5.5	Neg								
103–112	..	..	..	..	..	..	..	..	..	..	3.7	4.2								
113–120	..	..	..	..	..	..	..	..	..	..	4.7	3.5								
121–128	..	..	..	..	..	..	..	..	..	..	4.2	3.5								
129–138	..	..	..	..	..	..	..	..	..	..	3.7	3.7								
139–148	..	..	..	..	..	..	..	..	..	..	5.2	<1.0								
149–157	..	..	..	..	..	..	..	..	..	..	3.7	Bl.								
158–164	..	..	..	..	..	..	..	..	..	..	Neg	3.2								
165–171	..	..	..	..	..	..	..	..	..	..	3.7	Neg								
172–175	..	..	..	..	..	..	..	..	..	..	Neg	Neg								

* Calomel administered ** Calomel stopped Bl. Virus isolated on blind passage Neg. No virus found.

† For subjects 27-31, on stools collected 8 to 11 days after feeding of virus, top figures are for samples on eight day, while lower figures are for 9 to 11 day pool.

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Figure 2 summarizes antibody levels elicited in subjects of Group BB (Table 1) by feeding of virus. It will be noted that every child developed homotypic antibodies to the virus or viruses fed. The level of antibodies could not be correlated with the duration of the carrier state. This is illustrated by the contrasting titers of antibodies in the sera of subjects No. 17 (the highest) and No. 18 (the lowest). Both of these individuals excreted the SM strain for 164 to 171 days. (See Table 2.)

Subjects Nos. 15, 16 and 20 of the BB group (Table 1) received the Type 1 SM strain in the form of a gelatin capsule, whereas the remaining individuals of the group ingested the same virus in milk. This bypass of the pharyngeal region and upper alimentary tract had no influence upon either the rate and duration of alimentary infection (Table 2) or upon the development of homotypic antibodies (Figs. 2 and 3).

As mentioned before, all subjects

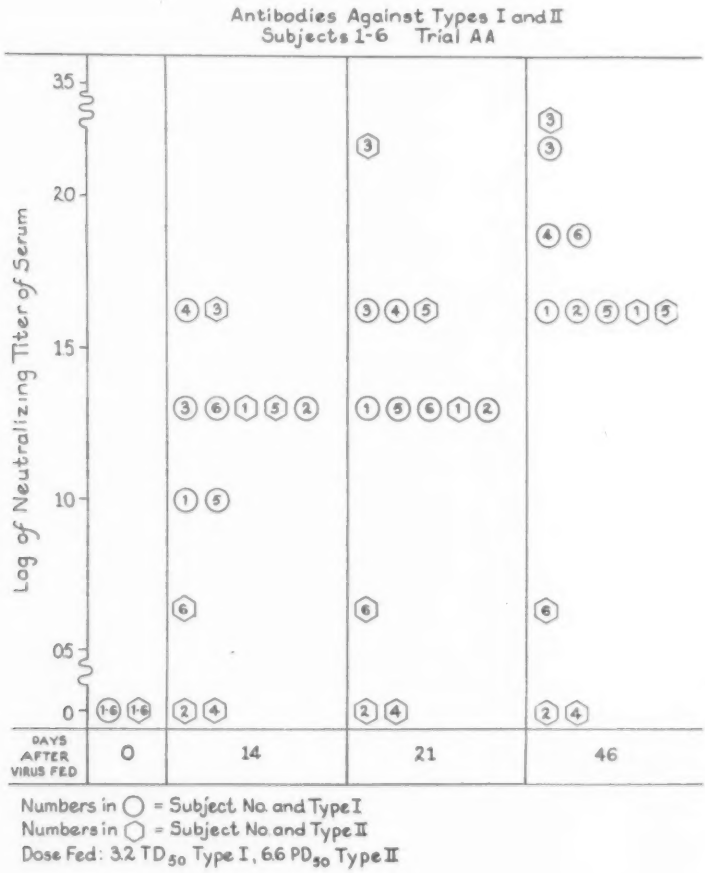

Fig. 1.

forming the BB group had their throats swabbed daily for 10 consecutive days following the virus ingestion. In not a single instance was Type I virus recovered from the swabs.

Figure 3 illustrates antibody response of subjects Nos. 19 and 20 of Group BB and of the 6 individuals in Group CC (Table 1). These subjects received Type I virus only, administered to all but No. 19 in capsule form. All developed homotypic antibodies.

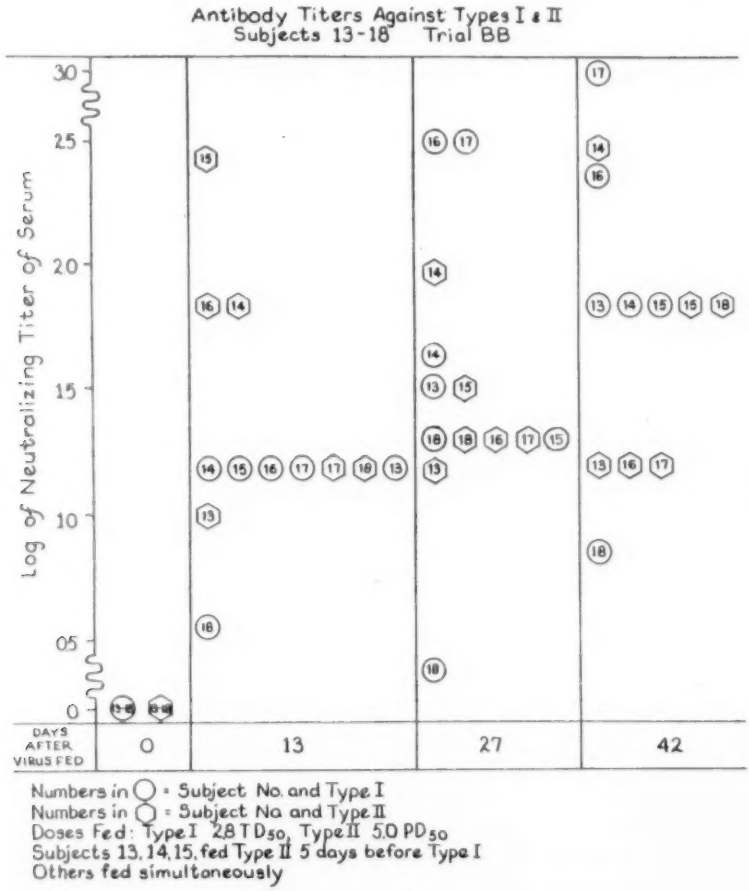

Fig. 2.

ATTEMPTS TO SUPPRESS ALIMENTARY EXCRETION OF VIRUS THROUGH CALOMEL MEDICATION. The effect of the administration of calomel upon the intestinal excretion of Type I (SM) virus is shown in Tables 3 and 4. It may be seen that stools of all subjects but one who received calomel within 10 days after feeding of the virus seemed to become free of virus within a short time after administration of the drug. The exception was subject No. 28, whose alimentary infection with virus remained essentially unaffected by calomel. The virus also reappeared in excretions of subject No. 27, but only

for a period of 2 days. When the drug was given 25 days after feeding of the virus (subjects Nos. 16 and 17), viral excretion was suppressed for 2 to 3 days and then the virus reappeared in the stool and continued to be excreted, in one case for 171 days. It is difficult to evaluate the role of calomel as a "virus suppressive agent," because of the irregular and nonuniform pattern of virus excretion in subjects who did not receive calomel. If a suppressive effect was observed in the BB and CC groups, it was not an "all or none" effect.

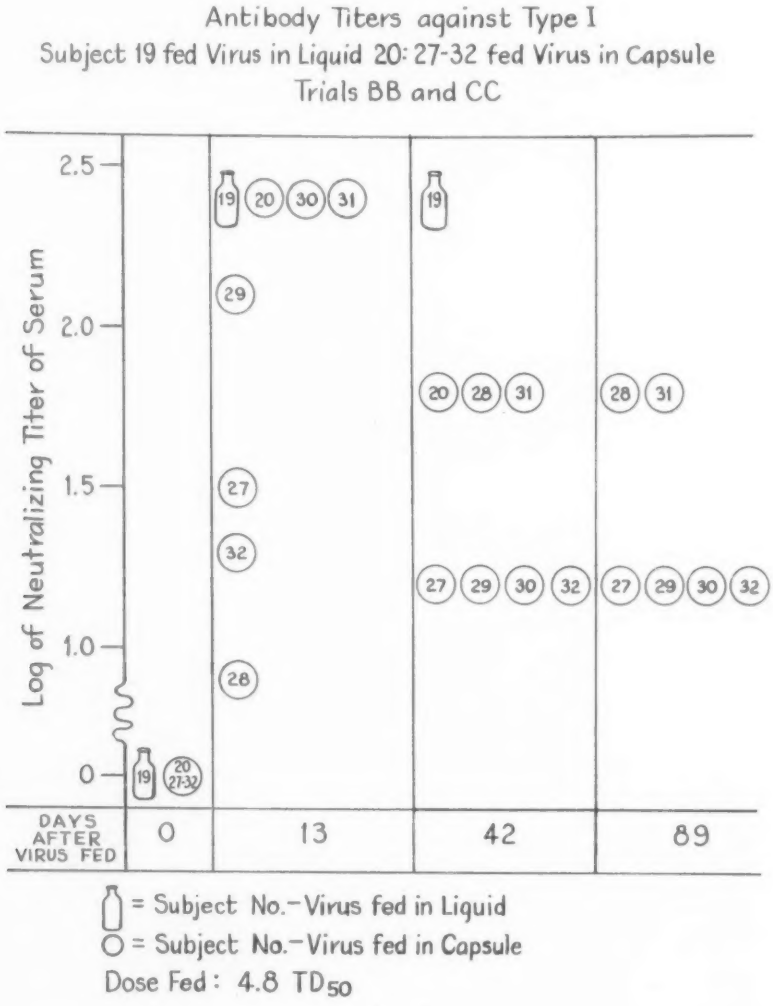

Fig. 3.

ATTEMPTS TO OVERCOME INTERFERENCE. Interference between Types I and II viruses had been noted in the preceding trials[3]. The interfering action of the SM (Type I) strain was again

apparent in the case of 3 subjects of group AA (Table 1). In an attempt to overcome this phenomenon, 6 subjects comprising part of group BB (Table 1) were divided into two subgroups. Three subjects received Type II virus 5 days before Type I. The other 3 subjects were fed the two viruses simultaneously. The results are shown in Table 5. Although separate administration of Types I and II resulted in antibody response to both viruses, the "control" 3 subjects (Nos. 16, 17 and 18) who received the "mixed" virus feeding also developed antibodies against both types. From the very scanty data obtained, it would appear that the separate administration of virus may have had a slight effect in shortening the duration of intestinal carriage of Type I virus in subjects Nos. 13, 14, and 15. Antibody levels, following simultaneous or separate administration of the two types of virus (Table 5) would seem to indicate that there was no significant difference in antibody response.

GAMMA GLOBULIN. Intramuscular administration of immune serum globulin just preceding or at the same time as the feeding of attenuated viruses seemed to be worth exploring. It was found that the administration of immune serum globulin to all subjects of the three trials did not significantly suppress the multiplication of virus in the intestinal tract, as evidenced by the prolonged excretion of virus in the stools of the subjects. The rate of alimentary infection and antibody development seemed to remain uninfluenced by the simultaneous administration of immune serum globulin.

Comment. Administration of the TN virus (Type II) to children in the present trial confirmed results obtained previously. From these results it appears that the TN strain is only rarely excreted in stools and then at very low concentrations. Type I (SM) strain was found in the alimentary excretions of every individual who ingested the virus. The basic difference between the viruses in their effect on the human alimentary tract may be related to the fact that one of the strains (TN) is

TABLE 3.—EFFECT OF CALOMEL ADMINISTRATION UPON INTESTINAL CARRIAGE OF SM (TYPE I) VIRUS

	Calomel Administration		*Intestinal Carriage of Virus*		
Subject No.	*Days after Virus*	*Mg. per Day × No. of Days*	*Absence** First Noted*	*Duration** of Absence*	*Reappearance** of Virus*
19	9–23	45 × 5 70 × 9	11	Permanent	
20*	9–20	45 × 5 70 × 6	10	Permanent	
16*	25–43	45 × 16	26	26–27	28–59
17	25–43	45 × 16	26	26–27	28–171
27*	7–15	70 × 1 45 × 7	12	12–22	23–25
28*	7–15	70 × 1 45 × 7	33	None 33–36	48*** 37–46
29*	7–13	45 × 6	12	Permanent	
30*	7	70 × 1	12	Permanent	
31*	7–15	70 × 8	15	Permanent	
32*	7–14	45 × 7	23	Permanent	

* Virus administered in gelatin capsule
** Days after administration of virus
*** Virus never absent from stool collection during 48 days of observation

TABLE 4.—CONCENTRATION OF SM (TYPE I) VIRUS IN FECAL MATERIAL OF SUBJECTS TREATED WITH CALOMEL AND OF UNTREATED CONTROLS

TD_{50} Titer per gm. of Fecal Material from Trial Subjects Receiving Treatment

Stools Collected and Pooled Days after Virus Fed	Trial BB Calomel								Untreated		Trial CC Calomel											
	19		20*		16*		17		13	18	27*		28*		29*		30*		31*		32*	
	B	A	B	A	B	A	B	A			B	A	B	A	B	A	B	A	B	A	B	A
1–3	4.7	..	5.7	..	5.2	..	5.5	..	6.2	6.5	4.5	..	4.8	..	5.7	..	4.7	..	0	..	4.5	..
4–6	4.7	..	4.7	..	+	..	6.7	..	+	5.2	5.2	..	6.2	..	5.5	..	5.5	..	3.5	..	4.7	..
8	..	0	..	0	..	..	..	..	..	N.T.	3.5	..	5.5	..	4.5	..	3.2	..	4.5	..	N.T.	..
10	..	0	..	0	+	..	+	..	+	+	N.T.	..	N.T.	..	N.T.	..	N.T.	..	N.T.	..	N.T.	..
9–11	..	0	..	0	5.7	..	+	..	6.8	+	..	3.2	..	5.2	..	4.7	..	Bl	..	5.2	..	3.2
12–14	..	0	..	0	4.7	..	5.7	..	5.5	5.5	..	0	..	4.2	..	0	..	0	..	Bl	..	Bl
15–21	..	0	..	0	5.5	..	5.2	..	5.7	5.2	..	0	..	+	..	0	..	0	..	0	..	+
22–25	..	0	..	0	Bl	..	Bl	..	Neg	Bl	..	0	..	+	..	0	..	0	..	0	..	0
26–29	..	..	..	..	..	Neg	..	Neg	Neg	Neg	..	0	..	+	..	0	..	0	..	0	..	0
30–32	..	..	..	..	..	3.5	..	5.5	Neg	Neg	..	..	..	+	..	..	..	..	..	0	..	0
33–46	..	..	..	..	..	4.7	..	4.5	Neg	3.7	..	..	..	+	..	..	..	..	..	..	..	..

B = Before administration of calomel
A = After administration of calomel
* = Virus administered in capsule

\+ = Virus present on direct inoculation but stool suspension not titrated
N.T. = Not tested, Bl = blind
NEG = No virus found

noncytopathogenic for epithelium and fibroblast tissue of either human or simian origin grown in tissue culture.

The successful immunization of children who received the Type I virus in capsule form indicates that the multiplication of the virus in the intestinal tract is a sufficiently strong stimulus to elicit antibody formation. Bypassing of the pharyngeal region may be indicated in order to eliminate one more source (mouth) of possible contagion.

Passive immunity produced by parenteral injection of human immune serum globulin had no effect upon the antibody response following the feeding of attenuated living poliomyelitis virus. In fact, the results show that antibody response compared favorably with that previously obtained without the use of the globulin[5]. It would appear, therefore, that human immune serum globulin could be used if desired as an added immunizing agent prior to or simultaneously with, the administration of poliomyelitis virus orally to man.

It was of interest to evaluate the effect of the administration of calomel upon the excretion of virus in stools. Obviously, the value of oral immunization would be considerably enhanced if a means were found to limit fecal excretion. Calomel was chosen as the drug of choice in attempting to suppress alimentary infection. LoGrippo *et al.*[7] had observed a suppressing effect by a mercurial compound upon the intestinal carrier state of mice exposed to Theiler's virus. Calomel has also had a long history of application in human medicine. In addition, Ward *et al.*[9] found that a mercury compound appeared to interfere with the excretion of poliomyelitis virus by humans.

TABLE 5.—EFFECT OF SEPARATE OR SIMULTANEOUS ORAL ADMINISTRATION OF TYPES I AND II OF VIRUS

Administration of Virus	*Dose*		*Subject No.*	*Duration of Intestinal Carriage**	*Antibody Response*	
	Type I	*Type II*			*Type I*	*Type II*
Simultaneous	3.2	6.6	1	1–59	+	+
			2	1–59, 66–70	+	—
			3	1–58	+	+
			4	1–49	+	—
			5	1–36, 45–53	+	+
			6	1–44, 55–59, 67–71	+	—
	2.6		16	1–25 † 28–59	+	+
	3.1	5.0	17	1–25 † 28–171	+	+
	3.1		18	1-20 35–162	+	+
Separate**	2.8		13	1–25	+	+
	2.8	5.0	14	1–24	+	+
	2.6		15	1–21	+	+

* Days after virus administration (Type I SM)
** The TN strain (Type II) administered 5 days before Type I
† Calomel administered on the 25th day

The results were equivocal. Perhaps this drug, at the dosage employed, showed some virucidal action upon the Type I strain used in the trial, especially when it was administered within a few days after ingestion of the virus. Its effect, however, was by no means constant, as shown by its conspicuous failure in several subjects. Attempts to find a more efficacious and less toxic drug are now in progress.

Summary. Twenty children, lacking antibodies to the type of virus admin-

istered, were fed either the attenuated Type I (SM) or Type II (TN) strain of poliomyelitis virus and injected simultaneously with human immune serum globulin. None showed any clinical signs of illness. The Type I (SM) virus was excreted by every individual; the Type II (TN) strain was rarely excreted. All children who ingested the Type I (SM) virus in capsule form developed the same level of antibodies as those fed the virus in milk. Throat swabs from these same individuals were negative. The administration of human immune serum globulin at the time of virus feeding had no effect on antibody response. The effect of calomel, used in an effort to suppress viral excretion in stools, was equivocal.

ACKNOWLEDGMENTS: The authors wish to express their appreciation for the co-operation of Mr. H. Von Bulow, Superintendent of the State Colony at Woodbine, New Jersey, and of Mrs. Margaret Heineman, R.N., Hospital Supervisor at that institution. Special thanks are due all the nurses who rendered assistance in the conduct of the study. In addition, the list of laboratory assistants, social workers, and office personnel who contributed their services is too long for individual acknowledgment; but to each of them we are profoundly grateful.

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SUMMARIO IN INTERLINGUA

Le Immunisation de Juveniles per le Alimentation de Vive Attenuate Virus de Poliomyelitis Typo I e Typo II e le Injection Intramuscular de Immun Globulina Seral

Virus de poliomyelitis typo I (SM) o typo II (TN) esseva alimentate a 20 juveniles non possedente anticorpores al typo administrate. Simultaneemente le subjectos recipeva injectiones de immun globulina seral human. Nulle del subjectos exhibiva signos clinic de morbo. Virus typo I (SM) esseva excernite per omne individuos. Virus typo II (TN) esseva excernite rarmente. Omne le juveniles qui ingereva virus typo I (SM) in le forma de capsulas disveloppava le mesme nivello de anticorpore como le juveniles qui recipeva le virus in lor lacte. Frottis de gurgite ab iste mesme individuos esseva negative. Le administration de immun globulina seral human al tempore del alimentation de virus habeva nulle effecto super le responsa anticorporee. Le effecto de calomel, usate con le objectivo de supprimer le excretion de virus in le feces, esseva equivoc.

OBSERVATIONS ON SOME POSSIBLE PRECURSORS OF ESSENTIAL HYPERTENSION AND CORONARY ARTERY DISEASE: V. HYPERCHOLESTEREMIA IN HEALTHY YOUNG ADULTS*†

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To be fashionable in the field of cholesterol today, one should either have a giant centrifuge or travel. This report may disappoint those who like to learn vicariously about the Bantus, the Eskimos, the Norwegians and the Japanese, for it is concerned entirely with people like ourselves. It is a simple appraisal of the differences in cholesterol levels to be found among medical students living in the same environment and of what these differences may mean. Ten years ago, while laying plans for a study of the precursors of hypertension and coronary artery disease, we were told that the cholesterol of normal subjects varies too much to mean anything. Despite this warning, cholesterol determinations were made on a class of medical students to see if the results looked promising. In that first class, the two subjects with the highest cholesterol values turned out to have family histories of considerable interest. The first subject, a 21-year-old with a cholesterol of 320 mg. per 100 ml., reported that his physician-father died of a heart attack at the age of 38, while making rounds at a hospital (Fig. 1). The subject's paternal grandfather also died of a heart attack a year later. The second subject had a cholesterol of 330 mg. per 100 ml. at the age of 24. At that time his parents were well as they neared the mid-fifties; both were obese (Fig. 2). A year later, his father had a "little stroke" with sudden onset of double vision while at work, which cleared up in a few days. Four years later he had a myocardial infarction. The subject's paternal grandfather died of his third coronary occlusion. Because we found an association between high blood cholesterol levels in sons and coronary disease in fathers and grandfathers, we continued to obtain cholesterol determinations. Now, 1000 determinations later, we can say that though cholesterol levels of normal subjects do vary widely, they *may* mean something!

Measurements of total serum cholesterol were carried out on successive classes of the Johns Hopkins medical students, by the Buell modification of the Bloor method as carried out in the Clinical Chemistry Laboratory of the Johns Hopkins Hospital. Fifty-three, or nearly 9%, of the first 612 subjects were found to have hypercholesteremia, with levels of 300 to 434 mg. per 100 ml. of blood. None of these subjects suffered from any of the diseases usually associated with high cholesterol values. Thirty-nine subjects had hypercholes-

*Read at the Sixty-ninth Annual Meeting of the Association of American Physicians, Atlantic City, New Jersey, May 1, 1956.

†This study was supported in part by Research Grants 215 and H–1891, the United States Public Health Service, Federal Security Agency, and in part by Research Contract V1001M–2768, Veterans Administration.

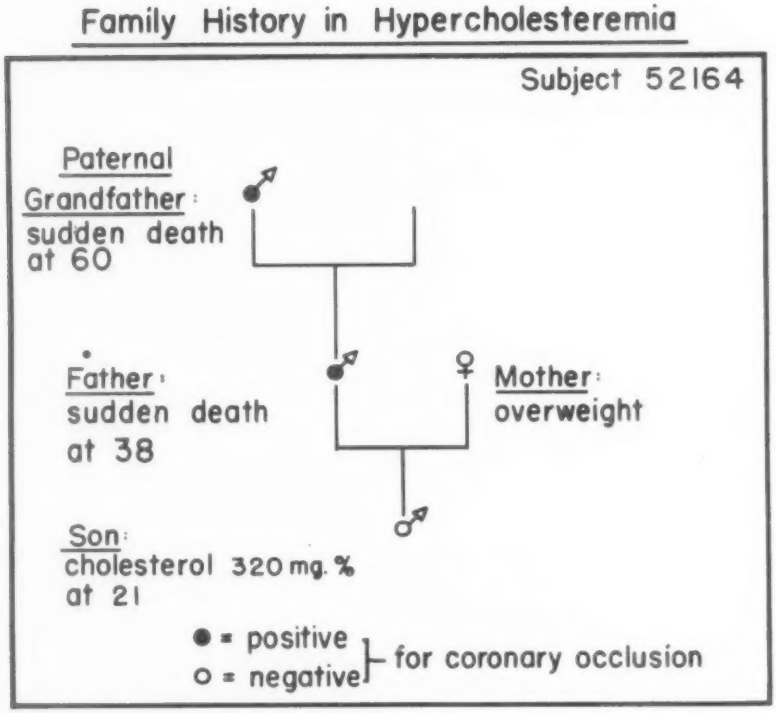
Family History in Hypercholesteremia
Subject 52164
Paternal Grandfather: sudden death at 60
Father: sudden death at 38
Mother: overweight
Son: cholesterol 320 mg. % at 21
● = positive
○ = negative
for coronary occlusion

Fig. 1.

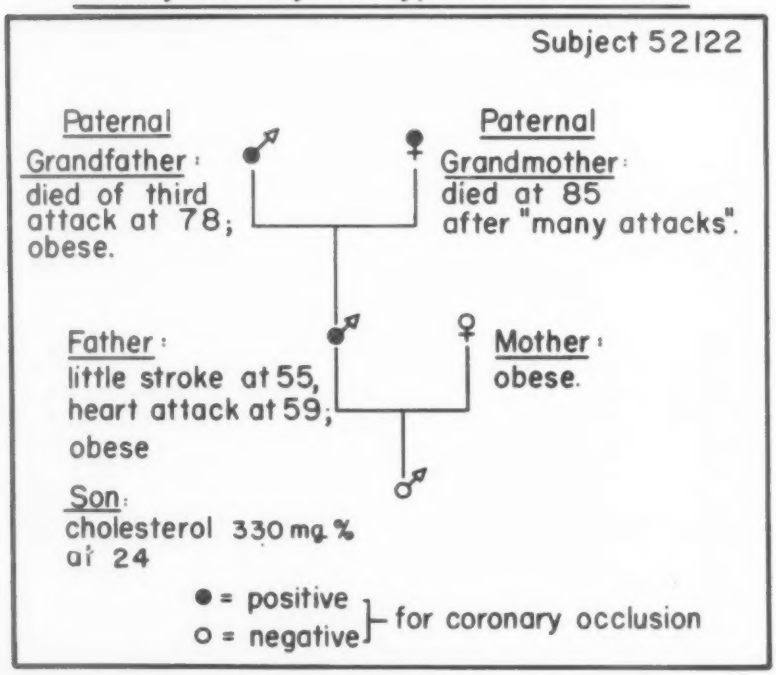
Family History in Hypercholesteremia
Subject 52122
Paternal Grandfather: died of third attack at 78; obese.
Paternal Grandmother: died at 85 after "many attacks".
Father: little stroke at 55, heart attack at 59; obese
Mother: obese.
Son: cholesterol 330 mg. % at 24
● = positive
○ = negative
for coronary occlusion

Fig. 2.

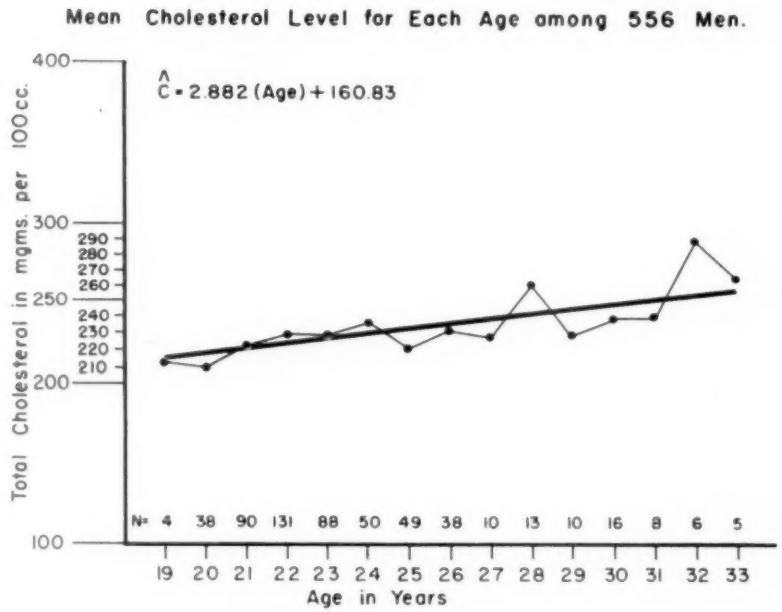
Mean Cholesterol Level for Each Age among 556 Men.
Ĉ = 2.882 (Age) + 160.83
Total Cholesterol in mgms. per 100 cc.
400
300
290
280
270
260
250
240
230
220
210
200
100
N= 4 38 90 131 88 50 49 38 10 13 10 16 8 6 5
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33
Age in Years

Fig. 3.

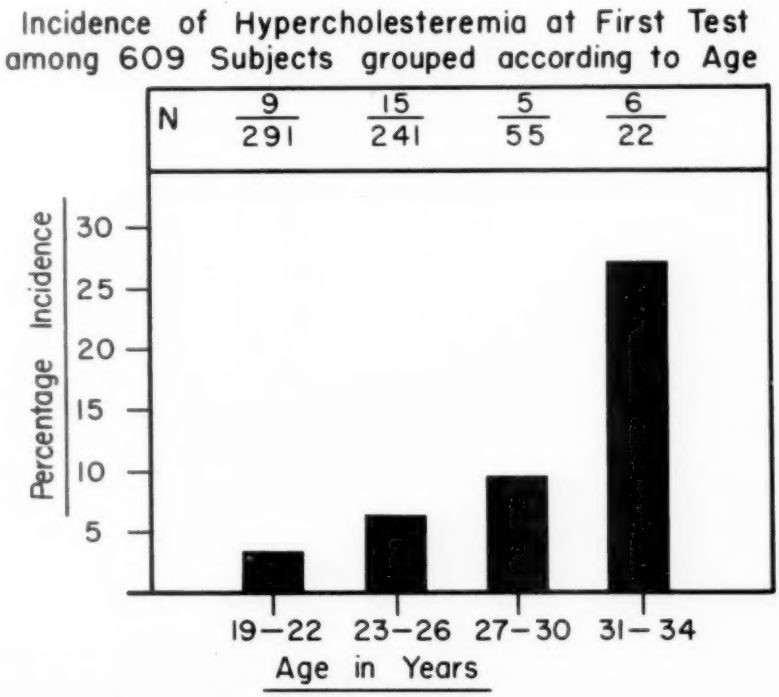
Incidence of Hypercholesteremia at First Test among 609 Subjects grouped according to Age
N 9/291 15/241 5/55 6/22
Percentage Incidence
30
25
20
15
10
5
19–22 23–26 27–30 31–34
Age in Years

Fig. 4.

teremia at the first test, while fourteen others developed it on subsequent determinations. These high levels occurred in both sexes and at all ages between 21 and 33, but not among the 42 subjects who were 19 and 20 years old. There was a slight rise in mean cholesterol with age, as has been found by Keys[4] and others, amounting to 2.88 mg. per year in our series[7] (Fig. 3). The rise in the early thirties (Fig. 4). This observation explains why additional hypercholesteremic individuals continued to appear as subjects were retested through medical school.

That age is not the only factor affecting the height of the cholesterol of a given student in medical school is suggested by a few determinations obtained several years after graduation.

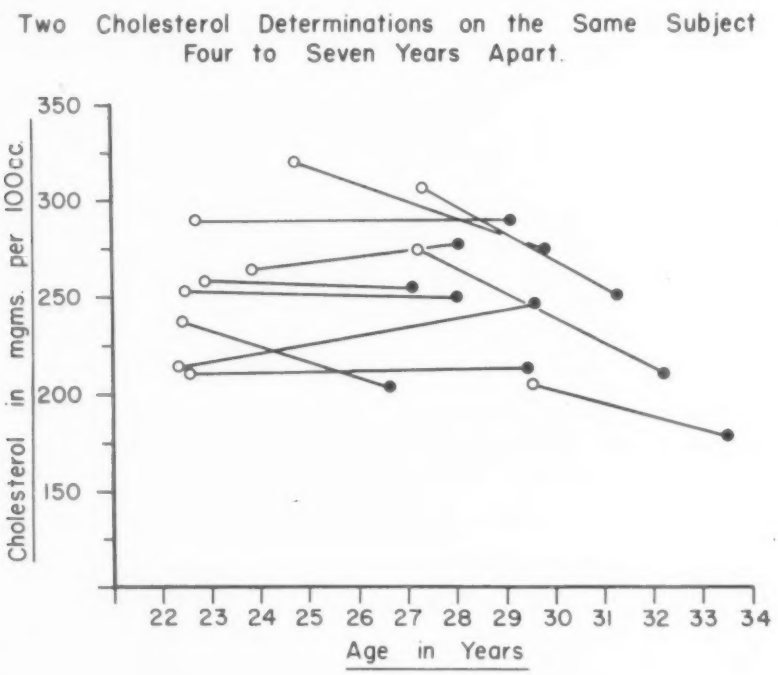

Fig. 5.

age gradient for men is given here; that of the 50 women was similar. The rise in mean cholesterol associated with age appears to come from altered proportions of those with high and low values, rather than from an aging effect in all individuals. The incidence of hypercholesteremia at first test increased steadily, from 3% among the 19 to 22-year-olds to 6% in the mid- and 9% in the late twenties, continuing to

Here is a comparison of two cholesterol levels taken 4 to 7 years apart on the same 11 individuals: four showed no change whatsoever, in five cholesterol decreased and in only two did it increase (Fig. 5). Moreover, changes of this magnitude frequently occur over much shorter periods of time. From these few observations one can only state that *not all* young adults show an increase of cholesterol with age, and

that in some the cholesterols may actually decrease. It seems likely that individual directional changes depend on many factors: changing habits of diet and exercise, the attainment of full growth, alterations in metabolic and endocrine activity associated with marriage, and perhaps most of all, variations in prolonged periods of stress, such as entering medical school, taking anatomy, marrying without money, obtaining a good internship.

jects (Fig. 6). The incidence of coronary disease among the fathers of hypercholesteremic subjects nearly tripled as the age of the subjects and their fathers increased, while there was little change among the fathers without this trait. The incidence among fathers of the subjects with normal cholesterol levels never quite equalled the lowest incidence found in the hypercholesteremic groups. Obesity was twice as frequent among the high cholesterol

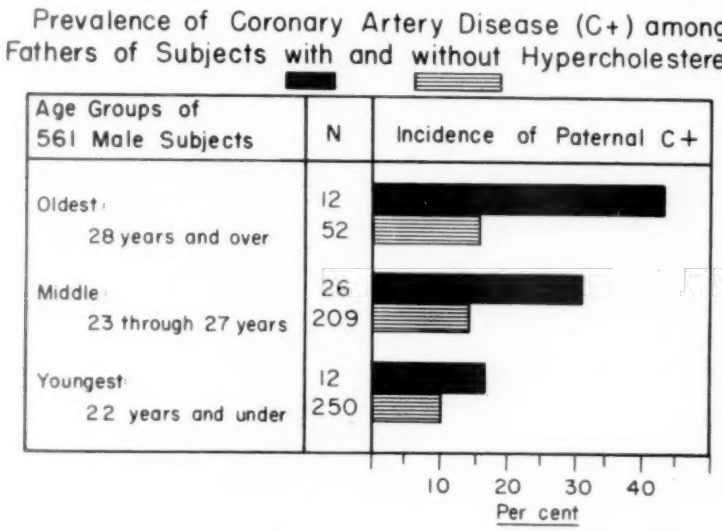

Fig. 6.

What characterizes these students with hypercholesteremia? First, they belong to families in which coronary disease, hypertension, diabetes and obesity appear with unusual frequency. The most striking finding was that 32.1% of the hypercholesteremic subjects had a parent affected by coronary disease in contrast to 11.8% of the 559 subjects with normal cholesterol values. This difference is highly significant statistically. Almost all the affected parents were fathers. The difference in the prevalence of paternal coronary disease was clear-cut in every age group of subfathers as was expected on the basis of the incidence in the normal group. Five of the 53 hypercholesteremic subjects reported parental diabetes, whereas only one or two would be expected to give such a history. Parental hypertension was somewhat more frequent in the hypercholesteremic group (Fig. 7). Unlike coronary disease, however, the increased prevalence was largely confined to the parents of the older subjects. Mothers particularly were affected, with high blood pressure appearing in the fifties. If this finding is confirmed in a larger series, it may

relate hypercholesteremia to that form of hypertension most often found as age increases, the arteriosclerotic type.

The medical history of the parents of the 53 hypercholesteremic subjects is summarized in Tables 1 and 2. The mean age of the fathers was 57 years. Attacks of various types were a prominent feature (Table 1). In addition to attacks of coronary occlusion and of angina pectoris, five fathers had "little strokes," involving sudden loss of consciousness, with or without convulsions and transitory impairment of the central nervous system. Blood pressure elevation was seldom great. Two fathers died of "nephritis" at an early age; the exact nature of the renal lesions is not known. More than half of the fathers suffered from one or more of the disorders indicated. The histories of the mothers at a mean age of 55 were somewhat different (Table 2). Coronary occlusion was rare, and never came alone. Two cases of hyperthyroidism and two of cardiac arrhythmias were reported, as well as two instances of mental disorder. One mother had an acute mesenteric thrombosis with infarction of the ileum. These assorted uncommon conditions may well be unconnected with the problem at hand, yet there were no comparable findings among the mothers of the other 559 subjects. Thus the parents of the 53 subjects with hypercholesteremia suffered from an unexpected number of medical disorders; many of these disorders were severe or fatal. In thirteen instances the presence of one or more of the four basic disorders in both parents was definite or probable. The same parent frequently suffered from several of the diseases in question, and these disorders have appeared increasingly as the years have gone on.

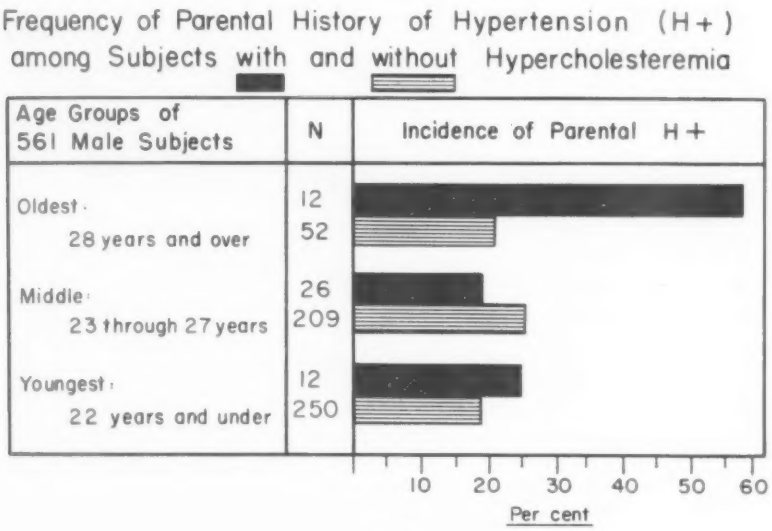

Fig. 7.

As a group, the disorders affecting the parents of the hypercholesteremic subjects are those described by Selye[6] as diseases of adaptation to stress, mediated by the adrenal cortex. Hypercholesteremia and coronary disease, as

well as hypertension, diabetes and obesity may occur in cases of adrenal cortical hyperplasia (Abbott *et al.*[1], Coone and Humphreys[2], and Plotz, Knowlton and Ragan[5]). It is known that cholesterol provides the building blocks for the corticosteroids. When something goes awry in the metabolic chain of events, adrenal cortical hyperplasia may appear. Wilkins and others[3] have postulated that the difficulty lies in the enzymatic biosynthesis of C_{21} steroids. The parallelism between the group of diseases manifested by the parents of the hypercholesteremic subjects and by patients with adrenal cortical hyperplasia suggests that a somewhat similar defect in adrenocortical metabolism may exist in the families under consideration.

Our preliminary findings raise many questions which are as yet unanswered. We do not know whether or not hypercholesteremia alone is actually a signal that atherosclerotic placques are being formed in the intimas of coronary arteries. A portion of the individuals who develop hypercholesteremia as young adults may show a return to normal values later on. It seems quite possible that in certain persons the most active period of atherogenesis may precede the actual moment of coronary thrombosis by an interval of years. Such a circumstance might account for the presence of normal blood cholesterol

TABLE 1.—MEDICAL HISTORY OF FATHERS OF 53 HYPERCHOLESTEREMIC SUBJECTS

Coronary artery disease (definite 16, probable 8)		24
Coronary occlusion (fatal 7, probable 2)	14	
Angina pectoris	4	
Cardiac arrhythmia; bundle branch block	3	
Heart failure	2	
Pulmonary embolism (fatal)	1	
Little strokes		5
Hypertension (definite 7, probable 4)		11
Obesity		11
Diabetes		4
Nephritis (fatal at ages 32 and 34)		2
AFFECTED BY ONE OR MORE DISORDERS		30
FREE FROM THESE DISORDERS		23

TABLE 2.—MEDICAL HISTORY OF MOTHERS OF 53 HYPERCHOLESTEREMIC SUBJECTS

Hypertension (1 with coronary occlusion)	10
Obesity	9
Diabetes (one transitory)	2
Diabetic retinitis without diabetes	1
Hyperthyroidism	2
Cardiac arrhythmias (atrial flutter, paroxysmal tachycardia)	2
Mental disorder (menopausal depression, nervous breakdown)	2
Acute mesenteric thrombosis	1
Accidental death	1
AFFECTED BY ONE OR MORE DISORDERS	23
FREE FROM THESE DISORDERS	30

levels in some patients with myocardial infarction. As the years go on, additional information about the parents as well as the students themselves may help to clarify these points.

Summary. These findings suggest:

1. That the emergence of the hypercholesteremic trait in young individuals can be linked with a familial tendency to cardiovascular disease, especially coronary disease, and to diabetes.

2. That hypercholesteremia makes its appearance at a time when physical growth and sexual maturity are complete, and when changing environmental factors may increase the cholesterol levels in some individuals but not in others.

3. That the persons who are susceptible to such environmental stresses probably inherit a metabolic defect, possibly of the adrenal cortex, which favors hypercholesteremia and atherogenesis and in time may lead to the development of coronary artery disease, hypertension, and diabetes, singly or in various combinations.

4. That hypercholesteremic young adults may be identified by periodic determinations of the serum cholesterol level.

5. That while measures directed toward maintaining normal cholesterol levels in these individuals might alter their subsequent disease patterns, they probably would not alter the fundamental metabolic defect.

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(Interlingua on page 457)

THE RELATIONSHIP BETWEEN EXCESSIVE CIGARETTE SMOKING AND PSYCHOLOGICAL TENSION

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Recent studies have clarified the deleterious effects of cigarette smoking. An association of the use of cigarettes with not only bronchogenic carcinoma (Hammond and Horn[8] and Wynder and Graham[15]) but also chronic bronchitis (Greene and Berkowitz[7], Joules[10] and Phillips *et al.*[12]) and coronary artery disease (Hammond and Horn[8]) has been pointed out. In spite of the wide publicity generally given to these studies in the lay press, an increase rather than decrease in cigarette consumption was reported for the year 1955. With a few exceptions, advice to stop cigarette smoking is disregarded by the individual patients whom one sees and the public at large as judged by the yearly sale of cigarettes.

It seems pertinent in view of the accumulated medical data to ask the question, "How can the smoking habit be broken?" Haphazard suggestions have been made but very probably no satisfactory answer to this will be forthcoming until more basic information is available as to why people smoke.

Among reasons for smoking listed by most authors is the mildly relaxing effect that a cigarette is subjectively observed to have. By implication, this suggestion points to psychological tension in the smoker as a major factor in the desire to smoke. In spite of the countless times that authors have associated nervousness and smoking, it is surprising to note that a survey of the literature since 1920 fails to reveal any data gathered to demonstrate this supposition. In fact, only four references to smoking were found in psychiatric literature (Bergler[2], Brill[3], Fenichel[6] and Hiller[9]). These authors appear unanimous in saying that smoking may be assumed to be a normal pleasure-seeking activity, except in cases of compulsion or in which it is elaborated into a pathological symbolic activity.

The present experiment sought to explore possible relationships between excessive cigarette smoking and presence of psychological tension. For this preliminary survey it was felt that study would have to be limited to those personal details that the subjects felt ready to admit freely. Psychological tension was defined as being evidenced by motor restlessness, exaggerated or inappropriate autonomic response, subjective worry and anxiety, and other purely psychological symptoms. It included both mild and severe forms of such symptoms and was not meant to apply only to clinically diagnosable emotional disorders. Consumption of more than one pack of cigarettes per day was considered excessive smoking.

Procedure. TESTS USED. Two questionnaires were used in this study. The first was the Cornell Medical Index, a 195-item questionnaire giving an estimate of the range of both

somatic (questionnaire pages 1 to 3) and psychological (page 4) symptoms. The second questionnaire was specially devised for this study and requested the patient to give the following information: number of jobs during the past 10 years and reasons for terminating employment; father's occupation, education, and marital history; brief description of the unhappiest time of his life; whether he had a happy childhood; and type, amount and duration of smoking. This questionnaire also contained the following:

Adjective Check List

The following words describe different kinds of people. Choose the 5 words that describe you best and mark them with a B. Choose the 5 words that describe you most poorly (those words that are *least* like you) and mark them with a P.

aggressive	confident
uncertain of myself	bashful
grouchy	calm
easygoing	trusting
suspicious	tough
even tempered	happy
cold person	quick tempered
sensitive	warm person
easily persuaded	nervous
bold	stubborn
relaxed	depressed
tense	agreeable

All the difficulties inherent in questionnaires were present in this study. A few of the patients were chosen to be interviewed and it was found that in the authors' judgment written responses by the patient tended to underestimate both the extent of their smoking and the extent of their psychopathology. There was no experimental attempt to compensate for this source of error. On the other hand, there is no reason to suspect that heavy smokers differed from others in the extent to which they underestimated their own psychopathology. Accordingly, the error should be a constant one and not affect the conclusions.

EXPERIMENTAL POPULATION. All persons tested were adult males in the Providence V. A. Hospital. Each of the six general medical and surgical wards was given questionnaires for distribution to its next ten consecutive new admissions. All bias of choice was thus eliminated, except that seriously ill or grossly handicapped patients were not included. It is not felt that this exclusion introduces any bias germane to the subject under study. It is known that neuropsychiatric patients differ from other hospital patients in their responses to the Cornell Index (namely, since the psychiatric patient has usually come to think of himself as emotionally disturbed, he is perhaps more willing to admit this on paper than an equally "nervous" individual who has never been a psychiatric patient). Accordingly, those patients whose records showed previous psychiatric diagnosis were eliminated. This left 53 questionnaires from male veterans never known to have been diagnosed as emotionally disturbed.

During analysis of the data it was found that only 14 of these 53 patients were classifiable as heavy smokers. In order to obtain a large enough group of heavy smokers, the medical histories of patients in all six wards were examined 2 months later and the first 10 heavy smokers found were chosen to fill out questionnaires. Thus, a final group of 39 "moderate smokers" and 24 "heavy smokers" was obtained. Moderate smokers were those who smoked one pack of cigarettes per day or less, including 15 who did not smoke cigarettes at all, while heavy smokers were those using more than one pack per day.

In addition, the two questionnaires were given to 32 neuropsychiatric patients, again consecutive admissions. These patients were nonpsychotic and were diagnosed either psychoneurosis or character disorder.

Results. In the manual for the Cornell Medical Index (Brodman, Erdmann and Wolff[4]) it is suggested that emotional disturbance be suspected if the total number of "Yes" responses is 30 or more, or if the number of "Yes" responses on the final page of the questionnaire (page 4 of the Index) is 3 or more. Table 1 indicates that the number of heavy smokers meeting these criteria is greater than the number of moderate smokers who do so. The differences in each case are statistically significant. Question number 166 asks the patient directly whether he is considered a nervous person. A much larger number of heavy smokers than of moderate smokers responded positively, and the difference is again statistically significant.

Table 2 indicates an analysis of the same data by the median test (Moses[11]). In this case, rather than choosing possibly emotionally disturb-

ed individuals by standard criteria, those with more positive responses are compared with those showing less such responses. This test indicates that for the entire Cornell Index and for each part separately, the heavy smokers tend to score in the pathological direction.

Because both the original 53 general medical-surgical patients and the 32 psychiatric patients were gathered at random, it was possible to compare the incidence of heavy smoking among the two groups. Table 3 shows this comparison: 50% of the psychiatric patients were heavy smokers while only 28% of the nonpsychiatric patients were. This difference is significant at the .01 level.

Responses to the special questionnaire often were not complete, and for this reason no analysis was possible for data relating to vocational history, "unhappiest time of life," or comparison between various achievements of father and son.

Table 4 lists three indices that were thought to be pertinent to the question of emotional health: marriage status, presence of psychosomatic diagnosis, and incidence of unhappy childhood. None of these personal data served to differentiate heavy smokers from moderate smokers.

TABLE 1.—COMPARISON OF SCORE OF HEAVY AND MODERATE SMOKERS BY CORNELL MEDICAL INDEX QUESTIONNAIRE

	Per cent Cases		*Chi-square*	*Probability*
	Moderate	*Heavy*		
Total score 30 or more	15	46	5.46	< .01
Page 4 score 3 or more	36	67	4.54	< .02
Question 166 positive	26	63	7.05	< .01

TABLE 2.—ANALYSIS OF COMPARISON OF SCORE OF HEAVY AND MODERATE SMOKERS BY CORNELL MEDICAL INDEX QUESTIONNAIRE

	Per cent Cases above Median			
	Moderate	*Heavy*	*Chi-square*	*Probability*
Total score	37	71	5.27	< .02
Pages 1–3	39	67	3.14	< .05
Page 4	39	67	3.14	< .05

TABLE 3.—AMOUNT OF SMOKING BY DIAGNOSIS

	Moderate	*Heavy*	*Total*
Psychiatric patients	16	16	32
Medical and surgical patients	38	15	53
Total	54	31	85
Chi-square = 7.41			
Probability < .01			

The results from the Adjective Check List are tabulated in Table 5. No hypotheses were made prior to gathering the data as to which words should be chosen most often by which group, and, as was expected, many words were completely nondiscriminating. In order to be able to work with trait names that were known to discriminate between emotional health and emotional illness, the 20 words that best differentiated the 32 psychiatric patients from the entire

group of 63 nonpsychiatric patients were chosen. As indicated in Table 5, fourteen "Best" and six "Poorest" descriptive words were chosen for final analysis. Of these 20 comparisons, six discriminated at the .05 level or better between heavy and moderate smokers, as indicated in Table 5. On the basis of chance alone, one would expect only one of the 20 to differentiate at the .05 level.

Another demonstration that a real difference exists between the two groups in the words they choose to describe themselves is provided by a non-parametric test (Wilcoxon's matched pairs signed ranks test[14]). The number of trait names which were chosen by moderate or heavy smokers in accordance with expectation, is 15, out of the possible 20 (indicated in Table 5, column labeled "Predicted Direction"). Using Wilcoxon's test, it is seen that such a large number of differences in the predicted direction should occur by chance alone less than once in 100 times. Thus even though only six traits differentiated significantly when taken separately, it seems likely that more comparisons would reach statistical sig-

TABLE 4.—MISCELLANEOUS INDICES

	Per cent Cases			
	Moderate	*Heavy*	*Chi-square*	*Probability*
Single and divorced	29	41	48	> .05
Psychosomatic diagnosis	26	41	96	> .05
Unhappy childhood	8	17	*	> .05

* Exact method for chi-square used (Edwards[5], p. 84).

TABLE 5.—ADJECTIVE CHECK LIST

	Per cent Cases Choosing Words as Best Description			
	Moderate	*Heavy*	*Predicted Direction*	*Probability*
Sensitive	12.1	23.8	yes	n.s.*
Agreeable	75.8	47.6	yes	.035
Happy	66.7	19.1	yes	.001
Nervous	3.0	38.1	yes	.035
Calm	27.3	19.1	yes	n.s.
Confident	27.3	38.1	no	n.s.
Uncertain of self	0.0	9.5	yes	n.s.
Bashful	18.2	19.1	no	n.s.
Easygoing	66.7	66.7		n.s.
Trusting	45.5	57.1	yes	n.s.
Quick-tempered	6.1	9.5	yes	n.s.
Tense	6.1	9.5	yes	n.s.
Stubborn	6.1	9.5	yes	n.s.
Relaxed	30.3	9.5	yes	.045
Poorest Description				
Relaxed	0.0	16.7	yes	.039†
Confident	3.2	5.6	yes	n.s.
Grouchy	74.4	38.9	yes	.017
Quick-tempered	32.3	38.9	no	n.s.
Cold person	29.1	44.4	yes	n.s.
Bashful	16.1	16.7	no	n.s.

* Not statistically significant.
† Exact method for chi-square used.

nificance if the number of subjects had been larger.

Discussion. The present data appear to indicate a very real tendency for this present group of heavy smokers to exceed the group of moderate smokers and abstainers in various indices relating to presence of "nervous" traits. In both number of somatic and psychological complaints, the heavy smokers seem to resemble the emotionally disturbed individual more than do the moderate smokers. In the manner in which they are willing to describe themselves, the heavy smokers are less agreeable, happy, and relaxed. On the other hand, they find it less difficult to think of themselves as nervous and grouchy than do moderate smokers. The fact that there was a greater number of heavy smokers in the psychiatric patient group than in the nonpsychiatic patient group would also support the notion that excessive smoking may be classed as a "nervous" habit. The only variables which failed to differentiate the groups were those that related most indirectly to nervous symptoms.

Because this experimental group was relatively small and from a select population, generalizations must be modest. Whether men, veterans, or physically ill people differ from other groups in the extent to which heavy and moderate smokers resemble each other is something that can be determined only by further study. However, it is difficult to conceive of maleness, illness, or veteran status, rather than extent of smoking, as being responsible for the observed differences. Likewise, it is difficult to conceive of another population with characteristics which would render it not susceptible to the same relationship between nervousness and heavy smoking.

It must be emphasized that it seems quite probable that any cause and effect relationship lies in the direction of excessive smoking being the result of nervousness, in the same general category with fingernail biting, thumb twiddling, and other restless motor activity. In the older literature on smoking (*cf.* bibliography in Schrumpf-Pierron[13]) there appeared frequent reference to tobacco as the cause of varied neuroses and psychoses. However, since 1920 there has been an almost complete absence of such references in the English and American literature. Brill[3] even goes so far as to say that he has never seen a neurosis or psychosis whose cause was attributable to tobacco smoking.

It is plain that the present results do not show that every heavy smoker is necessarily a nervous person. Of the 24 heavy smokers, there are 5 who are not shown to be above average in nervousness by any of the indices chosen. However, since these data depend so much upon the patient's own report, it cannot be assumed that all these patients were not in fact emotionally disturbed. The final answer to this question may be that while most heavy smokers tend to be nervous people, there are a variety of other reasons for heavy smoking which operate to a greater or lesser extent.

No attempt was made in the present study to determine whether pipe and cigar smoking are also associated with nervousness. Frequent testimonial references exist to the soothing qualities of pipes and cigars, but experimental confirmation has never been sought.

A crucial question is, perhaps, "Do moderate cigarette smokers differ from nonsmokers in amount of psychological tension?" This question was not adequately studied in the present investigation, although in a preliminary survey no significant differences appeared between 15 nonsmokers and 20 individuals who smoked one pack per day

or less. Further work is necessary to determine anything conclusive on this issue. It seems reasonable that some moderate smokers do smoke to "quiet their nerves." If it is a less frequent motivation for the light smoker than for the heavy smoker, it follows that a larger number of cases would be necessary to demonstrate a statistically significant association.

Summary. Among a group of 63 male veterans hospitalized for various medical or surgical conditions, the Cornell Medical Index indicated a wider range of somatic and psychological complaints in heavy smokers than in moderate smokers. The latter group described themselves on an Adjective Check List with personality trait names which relate to psychological normality, while the heavy smoking group tended to use the opposite kind of word. Among randomly chosen groups there was a significantly greater percentage of heavy smokers in a group of 32 psychiatric patients than among 53 nonpsychiatric patients. Heavy smokers were not differentiated from moderate smokers in marital status, judged happiness of childhood, or presence of psychosomatic disorder. It was concluded that there was an association between heavy smoking and presence of psychological tension.

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(Interlingua on page 414)

HAZARDS IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION*

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It is part of the natural history of discovery to find that enthusiasm for new methods and emotion often outstrip logic. This may explain in part the prevailing tendency to overtreat patients with acute myocardial infarction rather than otherwise. Although good medical practice even today can only be achieved by individual consideration of patients and treatment of each case according to its own merits, it is accepted procedure, in many quarters, to employ routine methods for all cases of this disease. Thus one finds, even among authorities, advocates of routine hospitalization and the routine use of morphine, oxygen and anticoagulants, supporters of routine quinidine therapy and proponents of routine "chair" treatment, early ambulation or prolonged bed rest. While many components of routine programs are extremely worthwhile, they lose their value or prove harmful when indiscriminately and at times unnecessarily employed.

After control of the initial pain which heralds the attack and the institution of bed rest, a large proportion of patients with acute myocardial infarction achieve uneventful recovery. In these uncomplicated cases, the physician need be little more than an attentive spectator of Nature's processes of healing and repair. In the more serious cases of acute coronary occlusion, on the other hand, the necessity of unerring judgment often presents a greater challenge to his ingenuity and skill than that entailed in the treatment of any other disease in clinical medicine. Nowhere may "minor" errors of omission or commission contribute as decisively to morbidity and mortality, yet in no disease is flexibility in therapy based on clinical evaluation of all the factors in the individual case more to be desired. Nowhere in the field of medicine may the responsibility for life or death rest more squarely on the shoulders of the attending physician, yet in no other situation is the response to conventional treatment more unpredictable. Indeed the aphorism "one man's food is another man's poison" could have no better application than to the management of this disease. Almost every form of treatment in acute coronary occlusion is associated with hazards arising from the therapy itself. Even with best intent and most correct practice, certain risks may be unavoidable and must be regarded as "the price that we, as responsible physicians, must pay for the inestimable benefits of modern . . . therapy."[2] In many instances untoward effects cannot be predicted in advance but often they can be anticipated, minimized or avoided by prudent management based on a safe yet comprehensive therapeutic philosophy. The use of potentially dangerous drugs may not be warranted for trivial complaints or for prophylaxis of purely theoretical value. The physician must therefore attempt to weigh the risk of every therapeutic measure against that of the complica-

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tion he is seeking to prevent or abolish. In acute coronary occlusion, perhaps more than in any other disease, discrimination in the choice of therapy is far more to be desired than academic completeness. Consequently an important aspect of the treatment of acute myocardial infarction that deserves continual circumspection is the harm that may ensue not only from the enlightened thoughtful use of therapeutic measures but also from therapy injudiciously or erroneously applied.

NITROGLYCERINE. Although nitroglycerine is the most useful drug in the management of angina pectoris and

TABLE 1.—HAZARDS IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION

Drug or Method	*Risks from Therapy*
Nitroglycerine	Precipitates or aggravates shock syndrome, reduces coronary flow and excites dangerous ectopic tachycardias.
Morphine	May produce abdominal distention, urinary retention, respiratory depression, vomiting and retching. Increases susceptibility to ventricular ectopic rhythms. Increases biliary pressure. Antidiuretic and hypotensive effects.
Oxygen	Adverse psychogenic effect (fear). Claustrophobia (tent). Hacking and coughing (nasal catheter). "Suffocation" and anxiety (mask). ? Ventricular fibrillation (100% oxygen).
Anticoagulants	Hemorrhagic complications and death. False sense of security (physician). Unnecessary or too early removal to hospital.
Hospitalization	Risk of ventricular fibrillation, cardiac asystole or shock from psychic and physical factors associated with removal to hospital especially during first 48 hours. Increased tendency to psychoneurosis and anxiety states.
Bed Rest	Loss of muscular and vascular tone. Constipation. Anxiety states. Thromboembolic complications.
"Chair" Treatment	Ventricular fibrillation, cardiac asystole, shock or cardiac rupture due to stress. Augments hypotensive effect of opiates. False sense of well-being (patient).
Digitalis	Intoxication more easily induced. Ventricular tachycardia. Atrial fibrillation (vagal effects). Ventricular fibrillation (if administered during ventricular tachycardia).
Quinidine	Vomiting, diarrhea and nausea common (orally). Cardiac arrest or ventricular fibrillation.
Pronestyl	Marked depressions of blood pressure. Ventricular fibrillation or cardiac arrest.
Pressor Agents	Excessive and dangerous elevations in blood pressure. May aggravate congestive heart failure. Local gangrene (Levophed).
Aminophylline	Palpitation, headache, nausea, chest pain, syncope collapse or death (intravenously).
Papaverine	Fall in blood pressure, collapse and fatal ventricular fibrillation (intravenously).
Alcohol	Increased heart rate. Ectopic beats. Paroxysmal tachycardia.

status anginosus it is manifestly dangerous in the presence of myocardial infarction. Nitroglycerine causes venous pooling in the lower extremities, diminished venous return to the heart, reduction in blood pressure and tachycardia. Evidence suggests that these actions of the drug may actually precipitate myocardial infarction when nitroglycerine is used to excess during a paroxysm of angina pectoris[12]. In acute coronary occlusion, on the other hand, even conventional dosage may precipitate or aggravate the shock syndrome by inducing a further drop in the blood pressure. In addition, this action of the drug may seriously reduce the coronary flow through the unoccluded vessels, in spite of vasodilatation, and excite dangerous ectopic tachycardias from reflex stimulation of the cardiac accelerators[7]. Since status anginosus may represent a premonitory phase of coronary occlusion, nitroglycerine must be employed with great caution where the latter is suspected. Fatalities attributed to the use of the drug at the onset of pain due to an acute myocardial infarction have been reported.

MORPHINE. For the relief of pain all physicians are agreed that morphine and other opiates are without equal. In the past an initial dose of no less than ½ grain of morphine was recommended routinely in the belief that smaller doses do no good and that substitutes are worthless. As a result of advances in the recognition of milder cases this dictum is no longer tenable. There would be no objection to the use of large doses of morphine to control the initial pain of acute myocardial infarction if such a routine were without danger. Actually morphine frequently complicates the course of coronary thrombosis by producing abdominal distention, urinary retention, respiratory depression, vomiting and retching. In addition the drug causes strong vagal stimulation rendering the heart more susceptible to ventricular ectopic rhythms; it increases biliary pressure and exerts an antidiuretic and hypotensive effect. In usual doses the drug has no action on the circulation in recumbent patients, but in the presence of acute myocardial infarction, if the head is elevated and feet dependent, it may precipitate a hypotensive syncopal attack or collapse[1]. Serious and even fatal results have been observed in patients with acute coronary occlusion who were given this drug and permitted shortly thereafter to assume an erect posture prior to removal to home or hospital. Large doses are occasionally necessary, as is intravenous administration, but mild pain can often be controlled by Demerol or codeine and in some cases even these are unnecessary.

OXYGEN. The value of oxygen in relieving dyspnea, cyanosis and cardiac pain when secondary generalized arterial anoxemia complicates myocardial infarction has been clearly established. There is no clear evidence, however, that oxygen even in high concentration exerts significant benefit in the management of patients sustaining an uncomplicated attack[10]. On the contrary, the psychogenic influences evoked by the administration of oxygen in patients afflicted with coronary thrombosis may prove a serious detriment. This is chiefly because the administration of oxygen to most patients carries the implication that they are critically ill. Furthermore, because of claustrophobia, some patients will not tolerate enclosure within a tent. Administration of oxygen by nasal catheter, on the other hand, frequently leads to irritation or inflammation of the pharynx which cause hacking and coughing, both undesirable efforts. Similarly, the use of a mask may produce a sense of

suffocation and a state of anxiety. Recent evidence also suggests the possiblity that inhalation of 100% oxygen may increase the tendency to ventricular fibrillation. Thus Beck[3] has shown that an electrically stable heart is a uniformly well oxygenated or a uniformly anoxic heart. According to this view the heart becomes electrically unstable and may fibrillate when the oxygen tension is not uniform throughout the myocardium. Differences in electrical potential are thus produced by differences in oxygen tension. The administration of 100% oxygen following acute coronary occlusion may, therefore, improve oxygenation of myocardium everywhere except in an area supplied by the obstructed vessel so that the oxygen differential produced may generate sufficient current to fibrillate the heart. This danger, if indeed it exists, is surely outweighed by the benefits derived from oxygen therapy in cases complicated by secondary generalized arterial anoxemia. In the uncomplicated attack, however, since even the high concentrations obtainable with a mask are of doubtful value to ischemic myocardium, any risk however theoretical, appears unwarranted. It would seem, therefore, that while oxygen should be freely employed when an indication for its use is recognized or even suspected, its continuation should be based on evidence of objective or subjective improvement of the symptom for which it was administered.

ANTICOAGULANTS. It appears to be established that the use of anticoagulant drugs represents an important advance in the treatment of acute myocardial infarction. It is well recognized, however, that there is a calculated risk in utilizing this form of treatment. Anticoagulants are contraindicated in the presence of 1) prothrombin deficiency (hypoprothrombinemia) due to vitamin K deficiency or severe liver disease, 2) blood dyscrasias with impairment of the normal mechanisms for hemostasis, 3) renal insufficiency, 4) vitamin C deficiency, 5) surgical or accidental trauma to the brain or spinal cord and 6) ulcers, malignant or benign, especially of the gastrointestinal and urinary tracts. Since the decision to use anticoagulants is usually made at the time of the first examination, exclusion of the conditions which contraindicate their use can, at best, be but cursory. In the hands of qualified investigators anticoagulant therapy has been responsible for 1.7 deaths in every 100 patients with acute myocardial infarction[15]. However, since the majority of patients are treated by general practitioners and not by specialists in research hospitals and since many patients are still being treated at home, it is important to translate this experience to the every day treatment of coronary disease in practice. The prophylactic value of anticoagulant therapy as well as the dangers from its use depend to a great extent upon the reliability of laboratory facilities, the conscientiousness and skill of the attending physician and the availability of vitamin K_1 and transfusions for emergency use. Even with meticulous care, however, the response of some patients is entirely unpredictable. Moreover, bleeding or thromboembolic complications may develop with the prothrombin time at "ideal" levels. Hemorrhage from anticoagulant therapy has been reported from almost every region of the body, but the brain, gastrointestinal tract and pericardium appear to be the commonest sites of fatal bleeding. With these dangers in mind, the physician must attempt to weigh the risk of therapy itself against that of thromboembolism in any given case. It has been adequately demonstrated that in severe attacks of myo-

cardial infarction, lives may be salvaged and disability prevented by the effective use of anticoagulant drugs. On the other hand, in mild or "good risk" cases* the incidence of thromboembolism is so low that no justification could be found for assuming the equal or greater risk from hemorrhage inherent in this form of treatment[13]. From the evidence, therefore, anticoagulants like other drugs appear to be indicated only under certain well defined circumstances. If the physician is not familiar with the action of these drugs or does not have the necessary laboratory facilities, he would be wise to abstain from their administration. If, on the other hand, he feels competent to apply such therapy, the condition of his patient should dictate his course of action.

HOSPITALIZATION. Since most attacks run a benign course followng the initial pain, the vast majority of patients can be treated at home if conditions there are satisfactory. If the patient's condition is serious, if nurses are not available or if the home environment is unsuitable, hospitalization should be recommended. The wide employment of anticoagulant drugs in acute coronary thrombosis has resulted in unnecessary risk arising from immediate hospitalization. In order to institute treatment without delay many patients are rushed to the hospital in spite of the fact that the highest death rate in this disease prevails during the first 48 hours. Since these early deaths are the result of ventricular fibrillation, cardiac asystole, shock or congestive heart failure, and are unrelated to thromboembolism, they almost certainly cannot be prevented by anticoagulant drugs. Obviously numerous factors may precipitate fibrillation in a hyperirritable ventricle, or stimulate cardio-inhibitory reflexes. These are thought to include physical activity, change in position, pain, mental strain, fear or other emotions, and stimuli from various organs in the body. The desire to save the small proportion who may die from thromboembolism after the first week may, therefore, jeopardize the chances for survival of the much larger segment of coronary cases known to die from other causes during the first 2 days. The author has been impressed with the relatively high incidence of early and sudden unexpected death even in mild cases hospitalized soon after the onset of the attack. The physical and emotional experience of an ambulance ride to the hospital, the psychic trauma of a hospital room and bed and of being placed in an oxygen tent, often when oxygen is entirely unnecessary, and the distress of repeated venipuncture for prothrombin and coagulation times may be hazardous during this early critical period. Any form of treatment, including anticoagulant therapy, can usually be initiated in the patient's home and removal to the hospital can be accomplished, if indicated, when apprehension has been allayed and these critical hours have passed.

BED REST. The tendency to reduce the bedfast time of patients with myocardial infarction appears to be a forward step in management. Prolonged bed rest in acute coronary occlusion and in heart failure is often unnecessary and indeed may be harmful. It has been shown that recumbency tends to increase cardiac work by increasing the circulating blood volume. Prolonged

*"Good risk" cases were those in which none of the following poor prognostic signs were observed on the day of admission to the hospital: 1) previous myocardial infarction; 2) intractable pain; 3) extreme degree or persistence of shock; 4) significant enlargement of the heart; 5) gallop rhythm; 6) congestive heart failure; 7) atrial fibrillation or flutter, ventricular tachycardia, or intraventricular block; and 8) diabetic acidosis or other states predisposing to thrombosis.

bed rest is frequently responsible for generalized loss of muscular and vascular tone, constipation and predisposition to venous thrombosis. It often has given rise to anxiety and prolonged psychoneurosis. The "chair" treatment of Levine[8] obviates some of these dangers and permits easier commode privileges. In the presence of dyspnea and pulmonary congestion the venous pooling produced by lowering of the legs may indeed be a desirable effect. The wisdom of utilizing "chair" treatment routinely from the onset of the attack as advocated by Levine, however, must be questioned. Considerably more than one-half of all the deaths in this disease occur during the first 2 days and, even in the mildest cases, a high proportion develop suddenly within the first 48 hours. As previously mentioned, these early fatalities are commonly the result of cardiac standstill, ventricular fibrillation, shock or congestive heart failure. Consequently although cardiac work may be less in the sitting than in the recumbent position, account has not been taken of the amount of strain that may be involved for the patient while being lifted or helped into a chair and back into bed. In our busy hospitals with limited personnel this procedure may not be devoid of stress for the patient. The hypotensive effect of the opiates when the head is elevated and the feet are dependent must also be considered when "chair" treatment is to be employed soon after the onset of the attack. It seems more reasonable, therefore, that the patient be disturbed as little as possible during the first few days of the illness. Sight must not be lost of the fact that dependency of the legs with the patient seated in a chair may predispose to thrombotic complications rather than prevent them. Numerous authors have recognized moreover that a tendency exists for patients nursed in this manner to take too light a view of their illness and to disregard protective restrictions. On the other hand, indiscriminate prolonged bed rest for all patients appears inadvisable[14]. It would seem, therefore, that the length of time in bed and the time for instituting "chair" treatment and ambulation can only be decided intelligently on an individual basis. The physical and psychologic state of each patient, not routine procedure, should determine how he can best be treated.

DIGITALIS. On theoretic grounds there has beeen hesitancy to use digitalis in the presence of a recent infarct lest it should favor rupture of the ventricle, increase the work of the heart, constrict the coronary vessels, induce serious arrhythmias, enhance the clotting tendency or dislodge cardiac thrombi. Clear-cut clinical proof that such harm may be produced, however, does not exist. Most authorities prescribe digitalis for the treatment of heart failure even in the first few days after myocardial infarction while recognizing that in the latter particular care is required to avoid intoxication from the drug. Since infarcted myocardium appears more irritable and more sensitive to digitalis, ventricular tachycardia with its dangerous potentialities may be evoked by injudicious use of the drug. As a precaution, therefore, digitalis is usually prescribed in somewhat smaller than conventional dosage for congestive heart failure complicating recent myocardial infarction. Only half the average dose or less is frequently effective in aged patients because of their greater sensitivity to digitalis than the young. The common manifestations of digitalis intoxication, nausea, vomiting and bigeminy, are well known. The earliest symptoms of overdosage however, are usually weakness, anorexia and abdominal pain. Premature beats and any other type of arrhythmia may develop.

for which the most effective antidote is potassium in oral or intravenous form. The possible occurrence of less common symptoms, such as diarrhea and visual disturbances should be kept in mind. Although valueless and even harmful in the treatment of traumatic or hemorrhagic shock, there is strong basis for the employment of digitalis in cardiogenic shock when signs of left ventricular failure have supervened. Digitalis has strong vagal effects, one of which may be the production of atrial fibrillation. Finally, it must be remembered that digitalis is potentially very dangerous in the presence of ventricular tachycardia since its administration for this arrhythmia uniformly results in ventricular fibrillation[5].

QUINIDINE. Quinidine is employed during the treatment of acute cardiac infarction to combat the development of numerous and troublesome premature contractions, persistent atrial flutter and fibrillation without cardiac failure and ventricular tachycardia. Quinidine is seldom capable of restoring sinus rhythm in the presence of severe failure and can add only a further hazard to recovery. The drug is definitely dangerous in the presence of complete heart block or intraventricular conduction defects. When ventricular tachycardia occurs in the course of acute myocardial infarction the gravity of the situation requires rapid therapy and larger doses than under other circumstances. If quinidine can be administered by mouth this is the preferred route. A dose of 0.6 gm. every 2 hours should be given with electrocardiographic control. Vomiting, diarrhea and nausea are common subsequent to quinidine administration and sometimes preclude its oral use. Tinnitus, vague psychic sensations and aberration of vision also occur. Parenteral administration of quinidine may be necessary when an acute arrhythmia is associated with collapse, unconsciousness, vomiting, or other factors that make oral use impossible or absorption from the gastrointestinal tract uncertain. The intramuscular route is the one of choice for parenteral administration. Intravenous quinidine should be used with the greatest reluctance. Doses as small as 0.2 gm. intravenously have proved fatal in susceptible individuals. The temptation to administer the drug too rapidly is great and once a toxic level is in the blood stream there is no retreat. Since its intravenous use is very hazardous it must be given extremely slowly either by an intermittent dose method or by dilution in a large volume of saline. The rate of administration recommended is not more than 0.1 gm. every 15 minutes up to and not exceeding 0.65 gm. Here electrocardiographic control is absolutely essential. When the QRS is prolonged by 50% or more, the quinidine must be stopped. When quinidine is pushed beyond this point the danger of cardiac arrest or ventricular fibrillation is imminent. When its administration is associated with sinus standstill, atrioventricular block, bundle branch block, a rise in ventricular rate, ventricular extrasystoles, ventricular tachycardia or transient ventricular fibrillation, the drug should be stopped. Oxygen and means for artificial respiration should be at hand during such therapy. Intravenous quinidine is very unpleasant to the patient often being associated with tinnitus, vague sensations of detachment, pallor and sweating. Although routine oral administration of quinidine in acute myocardial infarction has been recommended, no proof exists of its prophylactic value. Indeed the effect of the drug may depress sinus rhythmical activity and slow conduction so that ectopic premature systoles may actually be converted into ventricular tachycardia[5]. If the prema-

ture systoles tend to disappear then the quinidine may be continued. On the other hand, if a multiplicity of premature systoles develop, the drug must be immediately stopped. It is only by careful observation and electrocardiographic control that serious reactions and fatalities may be avoided during the use of this drug.

PRONESTYL HYDROCHLORIDE. This preparation is less toxic than quinidine and in usual therapeutic dosage does not produce the nausea, vomiting or diarrhea so common to that drug. Intravenously, it also appears much less hazardous than quinidine. For intravenous use, no more than 200 mg. should be given per minute, but up to 1000 mg. may be injected safely. Fatal ventricular fibrillation has resulted from as little as 0.2 gm. intravenously in a patient with ventricular tachycardia. Intravenous use of procaine amide is attended by profound depressions of blood pressure. To prevent this, Levophed may be administered simultaneously or Neo-Synephrine given as soon as indicated. As with quinidine, electrocardiographic control is desirable.

PRESSOR AGENTS. In the treatment of cardiogenic shock there is a place for the pressor drug which increases peripheral resistance and augments coronary flow without decreasing cardiac output, initiating serious arrhythmias or stimulating metabolism. Epinephrin which increases myocardial excitability is unsuitable but other pressor amines appear to be producing encouraging results. Levophed has become the most popular of these agents in the treatment of severely shocked patients and may reduce the mortality some 20%[4]. It must be given intravenously and is usually initiated in the dose of 4 mg. per liter of 5% glucose in water. This concentration is increased if necessary and the solution is given at a rate of flow capable of maintaining the systolic blood pressure at a level of 100 to 110 mm. Hg. During its use, the blood pressure should be recorded frequently not only to determine whether the dose is adequate but also to avoid an excessive and dangerous rise in blood pressure. If congestive failure is present, the amount of intravenous fluid administered with the drug must be curtailed. Extravasation of Levophed into the tissues may result in extensive areas of gangrene.

AMINOPHYLLINE. The slow intravenous injection of 0.5 gm. of aminophylline in 20 ml. solution may occasionally control pulmonary edema by relaxing the bronchial musculature. Such administration, however, is only rarely effective in relieving the pain of acute myocardial infarction. Aminophylline is the drug of choice when respiratory depression following the use of morphine is associated with Cheyne-Stokes respiration. Rapid intravenous injection of aminophylline may cause so much vasodilatation as to precipitate collapse or even death. Slower but still excessively rapid injection may cause lesser degrees of peripheral arteriolar dilatation resulting in palpitation, headache, nausea, chest pain and syncope. When given by the oral route it is doubtful that the drug has any other action than that of a diuretic.

PAPAVERINE. Papaverine has been recommended for cases of myocardial infarction because of its dilator action on the coronary arteries and its tendency to reduce or abolish premature contractions following experimental coronary ligation in dogs. Large doses, however, lead to A–V block and ventricular ectopic rhythm. Although papaverine is sometimes effective for the relief of pain when administered intravenously in doses of 1 to 1½ gr. diluted with 10 to 20 ml. of distilled water, it may produce a sharp drop in the blood

pressure, precipitate collapse and even fatal ventricular fibrillation. Exercise-electrocardiographic tests have demonstrated that massive single doses (4½ to 8 gr.) orally are necessary for favorable response in patients with angina pectoris[11]. Such dosage with its attendant side effects on smooth muscle precludes the use of this drug in acute myocardial infarction and other coronary disease states.

ALCOHOL. Whisky should not be given in acute coronary occlusion since it may increase the pulse rate, produce ectopic beats or precipitate paroxysmal tachycardia. Contrary to the view held for many years, alcohol is not a coronary vasodilator drug[9]. Its ability to relieve pain is purely the result of an analgesic action.

Conclusions. Adequate care for the patient suffering from acute coronary occlusion is one of the most urgent problems in present day therapeutics. Improvement in diagnostic methods and the introduction of a positive therapeutic program of active intervention in place of the older regimen of "masterful inactivity" have resulted in a reduction in the mortality rate in this disease from 50% to 20%. In spite of the major advances in diagnosis and therapy, however, it must still be recognized that under proper supervision a large proportion of these cases will run their course from beginning to end with little or no need for medication. Since hazards exist even with skillful use of therapeutic measures by competent physicians, overtreatment arising from the application of "routine" programs should be discouraged. It is only by adherence to the important principle of treating each patient individually that the dangers of indiscriminate therapy may be avoided. The use of potentially dangerous agents in acute coronary occlusion without clear indication is not justified. It is the physician's responsibility to be as aware of the hazards as the triumphs of modern therapy and to utilize such knowledge in the choice of specific measures for the individual case.

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INVESTIGATION OF THE SYNERGISM OF ISONICOTINIC ACID HYDRAZIDE AND CORTISONE. I. EFFECT OF ISONICOTINIC ACID ON THE METABOLISM OF CORTISONE BY LIVER TISSUE*

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Our interest in agents which potentiate the action of cortisone *in vivo* led us to study the synergism of para-aminobenzoic acid and cortisone clinically[7,9,10] and by *in vitro* methods[5]. Our search for other agents capable of potentiating the action of cortisone led us to investigate tetraethylthiuram disulphide[6] by clinical methods because the extreme insolubility of this compound in biologic fluids precluded its use in available *in vitro* tests.

Isonicotinic acid hydrazide (INH) attracted our attention because of its effects on microbial metabolism first shown by Neuberg and Forrest[3] and because of its inhibition of the spreading action of hyaluronidase in animal and human skin as demonstrated by Cappello and Vallegiani[1].

Since it is well known that the major site of cortisone inactivation is in the liver (Louchart and Jailer[2], and Schneider and Horstmann[4]), we decided to test the effect of INH on the metabolism of cortisone by liver tissue by an adaptation of the method of Schneider and Horstmann[4]. We modified this method by adding to the substrate in our test vessels INH in concentrations varying from 0.5 to 15 mg. Table 1 illustrates the conditions and results of a typical experiment. Figure 1 illustrates the results in all of our experiments.

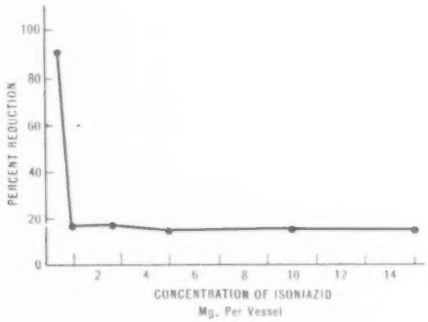

Fig. 1.—The effect of concentration of isoniazid on the amount of Compound E reduced.

As illustrated under the conditions imposed in these experiments between 88 and 89% of cortisone is inactivated after 3 hours of incubation with liver tissue slices in an oxygen atmosphere.

*This study has been aided by a grant from the A. H. Robins Co.

The addition of from 1.0 to 15 mg. of INH decreased inactivation to 18% in the same period of time under identical conditions.

It is of interest to note that like para-aminobenzoic acid, INH preserves the conjugated unsaturated system of the cortisone molecule as is demonstrated by the persistence of ultraviolet absorption, while side chain destruction is quite marked as shown by the fact that the Porter-Silber reaction fails to give measurable results. Chromatographic studies at present under way have produced at least one metabolite which is not identifiable by the usual methods.

These experiments suggest that INH should potentiate the action of cortisone *in vivo* by markedly inhibiting its destruction of the liver. This possibility has been explored clinically with encouraging results and is being reported in a separate communication[8].

Summary. The effect of isonicotinic acid hydrazide on the inactivation of cortisone by liver tissue was studied by a modification of the method of Schneider and Horstmann. In concentrations of 0.5 to 15 mg. per test vessel isonicotinic acid hydrazide strongly inhibited the inactivation of cortisone by liver slices. Isonicotinic acid hydrazide inhibits the hydroxilation of the conjugated unsaturated system of the cortisone molecule as shown by the persistence of the ultraviolet absorption curve but does not protect the side chain as shown by disappearance of the Porter-Silber reaction. These findings suggest that isonicotinic acid hydrazide should potentiate the action of cortisone *in vivo* by markedly retarding liver inactivation.

TABLE 1.—INCUBATION OF COMPOUND E AND ISONIAZID WITH RAT LIVER SLICES

	Ultraviolet Spectroscopy		
Vessel No.	*At 240 mμ*	*Average*	*Per Cent Reduction*
1—(B_1)	D	D	
2—(C_1)	.165	.167	
3—(C_2)	.170		
4—(E_1)	.020	.018	89.0
5—(E_2)	.015		
6—(EI_1)	.125	.121	18.2
7—(EI_2)	.118		

Blank vessel B_1 contained 15 mg. of isoniazid and 210 ± 2 mg. of rat liver slices in buffered solution. Control vessels (C_1) and (C_2) contained in addition 840 gamma of Compound E worked up without incubation. Vessels E_1 and E_2 containing the measured amount of Compound E in the tissue buffered solution were incubated for 3 hours in an oxygen atmosphere. Vessels (EI_1) and (EI_2) contained in addition to the measured amount of tissue and cortisone 15 mg. of isoniazid in buffered solutions. These vessels were treated in the same manner as vessels (E_1) and (E_2).

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SUMMARIO IN INTERLINGUA

Investigation del Synergismo de Isoniazido e Cortisona

1. Effecto de Isoniazido Super le Metabolismo de Cortisona per Histos Hepatic

Le effecto de isoniazido super le inactivation de cortisona per histos hepatic esseva studiate per un modification del methodo de Schneider e Horstmann. In concentrationes de 0,5 a 15 mg per vaso de essayo, isoniazido fortemente inhibiva le inactivation de cortisona per sectiones de hepate. Isoniazido inhibi le hydroxilation del conjugate systema non-saturate del molecula de cortisona, qual facto es demonstrate per le persistentia del curva de absorption ultraviolette, sed illo non protege le catena lateral, qual facto es demonstrate per le disparition del reaction Porter-Silber. Iste constatationes significa que isoniazido deberea esser capace a potentiar le action de cortisona in vivo per retardar marcatemente le effecto inactivante del hepate.

SUMMARIO IN INTERLINGUA

(See page 397 for original article)

Le Relation Inter le Excessive Fumar de Cigarrettas e Tension Psychologic

In un gruppo de 63 veteranos mascule, hospitalisate a causa de varie conditiones medical o chirurgic, le application del Indice Medical Cornell revelava un plus large varietate de molestias somatic e psychologic inter le forte que inter le leve fumatores. Ex un "Lista de Adjectivos Descriptive" le leve fumatores seligeva, como epithetos applicabile a illes mesme, tal designationes de tractos de personalitate que es associate con normalitate psychologic, durante que le gruppo del forte fumatores monstrava un tendentia a seliger le typo contrari de terminos. In duo gruppos, seligite al hasardo excepte que le 32 subjectos del prime esseva patientes psychiatric durante que le 53 subjectos del secunde esseva patientes non-psychiatric, il esseva trovate que le procentage de forte fumatores esseva significativemente plus alte inter le patientes psychiatric. Le forte fumatores non se differentiava ab le leve fumatores in relation a lor stato civil, lor judicamento subjective del felicitate de lor infantia, e le presentia o absentia de disordines psychosomatic. Esseva concludite que il existe un association inter le habitude del forte fumar e le presentia de tension psychologic.

INVESTIGATION OF THE SYNERGISM OF ISONICOTINIC ACID HYDRAZIDE AND CORTISONE. II. LONG-TERM STUDY OF THE SYNERGISTIC ACTION OF ISONICOTINIC ACID HYDRAZIDE AND CORTISONE ACETATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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Since the development of cortisone we have been interested in the intermediate metabolism of this hormone in the body and in agents which interfere with the intermediate steps in metabolism[11]. When our laboratory investigations showed that isonicotinic acid hydrazide (INH) was capable of inhibiting the hepatic inactivation of cortisone to an even greater extent than any other agent we had previously studied[10] we decided to test this finding in patients with active rheumatoid arthritis.

Much conflicting evidence has accumulated on the efficacy of cortisone and its analogs in the prolonged treatment of rheumatoid arthritis since it was first introduced. In contrast to the poor results obtained several years ago (Boland[1], Freyberg *et al.*[3], Levin *et al.*[5], Toone and Irby[7] and West and Newns[9]) more recent reports on its long-term use have been more favorable (Bunim[2] and Ward *et al.*[8]). Our own very satisfactory results with the prolonged administration of cortisone and synergistic agents in the treatment of rheumatoid arthritis have previously been reported[11] and have been confirmed by others (Homburger and Bonner[4], Oka[6], and Zarafonetis *et al.*[12,13]).

The present investigation was begun in May, 1953, and was conducted to evaluate the effect of a new synergistic agent, INH, in conjunction with small doses of cortisone acetate over long-term periods in order to eliminate the effect of spontaneous variations of disease activity.*

Method. A group of 39 patients with well-documented rheumatoid arthritis of more than one year's duration (with 3 exceptions) was selected for investigation. Some had previously been treated with corticosteroids but all exhibited definite clinical and laboratory evidence of active rheumatoid arthritis at the time of admission to this study group.

Since previous experience[11] had demonstrated that 37.5 mg. of cortisone acetate daily by mouth was insufficient in itself to suppress or to maintain suppression of active rheumatoid arthritis, this dose was arbitrarily

*A preliminary report was presented at the Annual Scientific Meeting of the New York Rheumatism Association in April, 1954.

selected. INH was concomitantly administered in doses ranging from 100 to 600 mg. per day with an average daily dose of 400 mg. This amounted to an average dose of from 5 to 8 mg. per kilogram of body weight per day. This dose of INH has been extensively used in the treatment of pulmonary tuberculosis and has been shown to be well tolerated in the vast majority of patients treated.

Each patient served as his own control by the withdrawal of either INH or cortisone acetate at irregular intervals. Withdrawal of the drug was always instituted at times when patients showed good clinical response in order to be able to judge and to correlate relapse with withdrawal. In the majority of patients both drugs were withheld at different times.

Results. A total of 39 patients have been so treated since May, 1953. In each patient we were able to demonstrate by the method used that INH definitely potentiated the anti-inflammatory effect of cortisone acetate since relapse during control periods was quite uniform irrespective of which of the two drugs was withdrawn. The only

TABLE 1.—RESULTS OF COMBINED ISONICOTINIC ACID HYDRAZIDE AND CORTISONE THERAPY IN 39 PATIENTS WITH RHEUMATOID ARTHRITIS

	Sex	*Age*	*Duration of Arthritis*	*Severity*		*Duration of INH and Cort.*	*Grade of Response*
				Grade	*Class*		
E.D.	F	54	4 yrs.	2	2	2 1/3 yrs.	2
E.F.	M	54	15 yrs.	4	4	1 1/6 yrs.	3
M.L.	F	65	1 yr.	1	2	10 mos.	1
L.F.	F	52	1 yr.	3	2	1 5/12 yrs.	2
J.Mc.	M	55	10 yrs.	3	2	1 1/4 yrs.	2
T.K.	F	55	10 yrs.	2	2	1 11/12 yrs.	Remission
J.V.	F	37	7 1/2 yrs.	3	3	1 1/12 yrs.	2
G.H.	F	46	5 yrs.	4	2	1 3/4 yrs.	2
M.S.	F	44	4 yrs.	3	2	1 1/12 yrs.	Remission
L.K.	F	39	1 yr.	2	1	5 mos.	Remission
E.L.	F	59	8 yrs.	2	2	1 mo.	2
L.G.	F	25	1 yr.	3	2	1 7/12 yrs.	2
V.A.	M	72	1 yr.	2	2	2 1/2 mos.	2
M.F.	F	63	3 yrs.	4	4	1 1/16 yrs.	3
J.M.	M	60	2 yrs.	3	2	3 mos.	2
A.D.	F	68	10 yrs.	2	2	2 mos.	2
R.B.	F	44	24 yrs.	3	3	6 mos.	2*
A.G.	F	53	6 yrs.	3	3	1 1/12 yrs.	2
C.R.	F	25	2 yrs.	1	2	1 yr.	2
F.L.	F	32	7 yrs.	2	2	5 mos.	2
M.L.	F	38	2 yrs.	3	2	1 1/6 yrs.	2
C.L.	M	33	2 mos.	3	2	5/12 yr.	2
D.L.	F	52	7 yrs.	3	2	1 3/4 yrs.	2
J.McD.	M	48	2 mos.	2	2	5/12 yrs.	2
G.M.	F	47	1 yr.	2	2	1/6 yr.	2
D.P.	F	65	20 yrs.	4	4	1 11/12 yrs.	3
D.R.	F	28	14 yrs.	4	3	2 1/4 yrs.	2
V.R.	F	33	3 mos.	2	2	1/6 yr.	2
G.S.	F	43	16 yrs.	3	3	1/2 yr.	2
J.A.	F	33	1 yr.	2	2	1 1/6 yrs.	2
M.A.	F	46	5 yrs.	2	3	2 1/3 yrs.	2
G.B.	F	35	1 yr.	3	2	1 1/12 yrs.	2
F.C.	F	48	18 yrs.	2	2	2 yrs.	2
H.C.	F	49	5 yrs.	3	2	2 1/3 yrs.	2
R.D.	F	56	5 yrs.	3	3	2 yrs.	2
N.F.	F	36	8 yrs.	2	2	10/12 yr.	2
B.G.	M	48	3 yrs.	2	2	2 1/4 yrs.	2
S.G.	F	37	4 yrs.	4	4	2 1/12 yrs.	2
K.G.	F	28	14 yrs.	3	3	2 1/6 yrs.	2

* This patient developed paresthesia of the legs.
The line separates clinic from private patients.

exceptions to this were 3 patients in whom complete remission of disease occurred after a period of treatment. In these patients no return of activity has occurred to date in spite of cessation of all treatment.

The combination was well tolerated. It produced increased appetite and mild euphoria as previously noted in the treatment of tuberculosis with INH alone. The only side reaction observed apart from weight gain (which was never excessive) was mild facial rounding. In one patient paresthesia of the lower extremities developed but cleared on the administration of pyridoxine hydrochloride. It should be added that this combination was administered to diabetic patients without increase in their insulin requirements as well as to hypertensive patients without increase in their hypertension. Table 1 summarizes the significant data in this group of patients. The degree of involvement and response to therapy are graded in terms of the standards of the American Rheumatism Association.

As a whole, these results have been highly favorable since this combination of drugs produced desirable suppression of clinical activity in a great majority of the patients without serious side reactions even in those individuals who were suffering from complicating disease. We have been able to continue this treatment for periods in excess of one year in 24 patients and in excess of 2 years in 9 patients. We stopped this treatment in one patient because of the development of paresthesia.

Discussion. Publication of the results here presented were purposely delayed in order to permit satisfactory evaluation of synergism over a period of time sufficient to eliminate coincidental improvement as well as the acknowledged vagaries of this disease. The findings have been so consistent and reproducible as to eliminate any doubt as to their validity. They lend further support to the well established fact that the corticosteroids are destroyed largely by the liver and to a lesser extent by the spleen and kidney. Any substance which interferes with this destruction either by competing for the underlying enzymatic mechanisms or by interfering with the enzymatic mechanism itself or with its coenzyme system will retard destruction of administered cortisone and increase the persistence of its effect in the body.

This prolonged "life" of a given amount of the steroid seems to increase its therapeutic activity without at the same time producing the undesirable side reactions noted with doses of cortisone large enough in themselves to produce equal anti-inflammatory activity. Satisfactory explanation of this observation must await explanation of the mechanism of action of the steroids in inflammation. The only possible explanation at this time is that smaller doses act in a more physiologic fashion while large doses produce a pharmacologic effect with accompanying manifestations of an undesirable nature.

It is to be anticipated that a final elucidation of the mechanisms of the anti-inflammatory action of the corticosteroids will in all probability remove them from the role which they now play in the therapy of inflammatory disease. This in turn will permit the development of other agents which will produce anti-inflammatory effects without the undesirable side reactions associated with large doses of corticosteroids. Investigation in this direction is being pursued in this laboratory.

Results of tests with the newer synthetic corticosteroids, prednisone, prednisolone and the 9-alpha substituted hydrocortisone in conjunction with INH are to be published separately. In general they do not differ from those

obtained with cortisone acetate and INH.

Summary. The demonstration of the inhibition of cortisone inactivation by liver tissue in the presence of isonicotinic acid hydrazide prompted the testing of clinical synergism of this combination. An average daily dose of 400 mg. of INH and 37.5 mg. of cortisone was administered to a group of well-documented cases of rheumatoid arthritis. The effectiveness of this combination was proven by alternate withdrawal of INH or cortisone. The combination proved effective while neither drug by itself was adequate for control of arthritic manifestations in the dosage employed. This form of therapy was satisfactory and free of the side reactions which occur with large doses of cortisone alone. Similar studies with the newer synthetic derivatives of cortisone are under way.

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SUMMARIO IN INTERLINGUA

Investigation del Synergismo de Isoniazido e Cortisona
II. Studio a Longe Duration del Action Synergic de Isoniazido e Acetato de Cortisona in le Tractamento de Arthritis Rheumatoide

Le demonstration del inhibition manifeste in le presentia de isoniazido in le inactivation de cortisona per histos hepatic inspirava le probation del synergismo clinic del duo mentionate substantias. Un dose diurne median de 400 mg de isoniazido plus 37,5 mg de cortisona esseva administrate a un gruppo de ben documentate casos de arthritis rheumatoide. Le efficacia del combination esseva demonstrate per le abstention in alternation de isoniazido e cortisona. Le combination se provava efficace durante que ni le un ni le altere del drogas per se esseva adequate pro le controlo del manifestationes arthritic in le doses empleate. Le therapia combinate esseva satisfactori e libere del reactiones lateral que occurre con administrationes de grande doses de cortisona sol. Simile studios con le plus recente derivatos synthetic de cortisona es in progresso.

URINARY GONADOTROPHIN EXCRETION IN OSTEOARTHRITIS

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Pituitary overactivity has long been suspected as an etiologic factor in primary osteoarthritis arising after the menopause. Excess pituitary growth hormone has been particularly suspected although it has never been demonstrated. Suspicion may also be directed to gonadotrophins since these are produced in excess after the menopause[1]. Also, chorionic gonadotrophins are known to stimulate skeletal growth in prepubertal years, and under certain conditions are capable of producing degeneration of articular cartilage in animals[4].

Recently we observed a case of arthritis mutilans in which the cartilaginous lesions had repeatedly flared up upon

24-HOUR URINE ASSAY IN OSTEOARTHRITIS CASES

Patient	*Age (Years)*	*Years Postmenopausal*	*Gonadotrophins (Mouse Units)*
1.	68	15	110
2.	65	15	125
3.	61	21	125
4.	56	9	336
5.	56	30	250
6.	38	2	125
7.	60	17	125
8	58	15	354
9.	71	21	620
10.	66	21	500
AVERAGE	59.9	16.6	267

24-HOUR URINE ASSAY IN NONARTHRITIC CONTROLS

Patient	*Age (Years)*	*Years Postmenopausal*	*Gonadotrophins (Mouse Units)*
1.	64	14	122
2.	65	15	150
3.	64	20	200
4.	54	5	696
5.	63	10	117
6.	50	4	100
7.	59	11	300
8.	55	13	318
9.	70	18	225
10.	65	12	108
AVERAGE	60.9	12.2	233.6

the injudicious administration of chorionic gonadotrophins[3]. Since cartilage destruction occurs in both osteoarthritis and arthritis mutilans, it seemed worthwhile to find whether osteoarthritic patients showed excess gonadotrophin excretion.

Methods. Ten postmenopausal patients were selected who had osteoarthritis involving the proximal and distal interphalangeal and other joints. In these cases the diagnosis was certified by several members of our arthritis clinic, all had confirming roentgenograms, and in no case was there any doubt as to co-existing traumatic or rheumatoid arthritis. A similar number of women of corresponding ages and postmenopausal intervals who showed no clinical or radiological evidence of osteoarthritis were selected as controls. The average age of the osteoarthritis group was 59.9 years with a 16.6 year postmenopausal period: Nonarthritic controls average 60.9 years with an average of 12.2 years after the menopause.

Twenty-four hour urine specimens were collected in clean containers, kept cool and promptly delivered to the laboratory. Gonadotrophins were assayed by the uterine weight increase method of Levin and Tyndale[2] and the results reported in mouse units. Serial dilutions of 1:3, 1:6, and 1:10 were performed and further "run out" on those specimens whose values were elevated above the usual range. (Usual premenopausal range 0 to 35; postmenopausal 90 to 300 mouse units.)

Results. Excretion of corticoids, 17-ketosteroids and estrogens was determined in each case of osteoarthritis. No consistent deviations from normal were observed.

The gonadotrophin assays are tabulated on page 419.

Conclusion. Pituitary gonadotrophin excretion was almost identical in the series of 10 cases of osteoarthritis and the series of 10 carefully matched controls. It may, therefore, be assumed that the amount of gonadotrophins, as measured by current techniques, is not a factor in the etiology of osteoarthritis.

ACKNOWLEDGMENT: We wish to thank Mr. Harry E. Hadd, M.Sc., for technical assistance in laboratory determinations.

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SUMMARIO IN INTERLINGUA

Excretion Urinari de Gonadotrophina in Osteoarthritis

Le excretion de gonadotrophina pituitari esseva quasi identic in un serie de 10 casos de osteoarthritis e un serie de 10 cautemente seligite subjectos de controlo. Ergo le conclusion es justificate que le quantitates de gonadotrophina mesurabile per le technicas currentemente in uso non constitue un factor in le etiologia de osteoarthritis.

VASCULAR HEMOPHILIA: THE ASSOCIATION OF A VASCULAR DEFECT WITH A DEFICIENCY OF ANTIHEMOPHILIC GLOBULIN*

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An hereditary hemorrhagic disorder which has certain features in common with hemophilia but differs from it in many respects, has been called by several different names. These include thrombopathia v. Willebrand-Jürgens or v. Willebrand's syndrome, pseudohemophilia, vascular hemophilia and female hemophilia. The condition was originally described by v. Willebrand and Jürgens[34] and its features have been amplified further by several subsequent investigations (Estren, Sanchez and Dameshek[7], Revol, Favre-Gilly and Ollaguier[26]). The natural history, symptomatology, and routine laboratory findings are well defined, and the disorder can be considered a clinical entity.

Both males and females are affected. The heredity follows a dominant pattern although sporadic cases occasionally occur (Revol, Favre-Gilly and Ollaguier[26]). The first symptoms usually appear in early childhood but may be delayed until puberty. Epistaxis is the most common manifestation and sometimes the only spontaneously occurring hemorrhage. Bleeding from the gums is frequent and prolonged bleeding may follow small lacerations and surgical procedures. Easy bruising with spotty ecchymoses and subcutaneous hematomas are frequent. Petechiae occur but are less common. Profuse bleeding from the uterus during or between the menstrual periods is not infrequent and postpartum hemorrhage has been described. Gross bleeding into the gastrointestinal tract is unusual and the occurrence of hemarthrosis is rare. Typically, the bleeding tendency fluctuates with periodic exacerbations and remissions. Females are often more severely affected than males. Of the 48 patients with clinical symptoms reported by v. Willebrand and Jürgens[34] ten females died from either nose bleeds, uterine bleeding, posttraumatic hemorrhage or gastrointestinal hemorrhage. With increasing age the disease becomes less severe.

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Routine laboratory studies reveal a normal clotting time, Quick prothrombin time, platelet count and clot retaction. The most common abnormality is a moderately to markedly prolonged bleeding time. The Rumpel-Leede test is strongly positive in the severe cases while in milder cases it can be normal in spite of a prolonged bleeding time. From the information available it is not yet clear whether the syndrome represents a pathogenetic entity or whether different conditions are manifested by a clinically similar bleeding disorder. The cases described in the present study fulfill the clinical criteria for the diagnosis of pseudohemophilia. Laboratory studies have shown them to have a vascular defect together with a deficiency in antihemophilic globulin. The significance of these findings will be discussed.

Clinical Data. Information concerning 5 families with this hemorrhagic disorder is reported. There is no evidence that these families are interrelated. In 34 individuals an increased bleeding tendency was assumed from either the history or clinical and laboratory findings. Twenty-eight individuals were studied in our laboratory and 8 patients of the 5 families were investigated in detail (Figs. 1 to 3).

FAMILY C. This family is of particular interest, since the clinical course has been severe in two siblings, both of whom have been studied in detail. Historical data on 39 family members were obtained. It was not possible to obtain convincing evidence of the hereditary occurrence of a hemorrhagic disorder, except for a questionable history of childhood nose bleeds in three family members and the finding of a strongly positive tourniquet test in the mother of the two siblings whose histories are presented in detail:

GG (A), a 7-year-old girl, suffered from moderate to severe epistaxis since early childhood. Bleeding from decaying teeth, from the gums and adenoids and after tooth extraction has occurred repeatedly. Hemorrhage from the gastrointestinal tract resulted in iron deficiency anemia. Bleeding was prolonged after cuts and small lacerations. She had a marked tendency to bruise easily and was always covered with a variable number of ecchymoses and subcutaneous hematomas. Many of these had the central firm white node with halo of blue pigment often seen in hemophilia. Blood transfusions were necessary on three occasions and were effective in reducing bleeding.

TG (B) had suffered from intermittent epistaxis since early childhood. These bouts occurred about fifteen times per year and each lasted from 10 hours to 2 days. At the age of 3½ years such an episode could not be controlled and the patient expired. Necropsy revealed no cause for death other than acute blood loss. Tests reported on the chart included bleeding times of 24 and 27 minutes, a negative tourniquet test, and a venous clotting time of 7 minutes.

FAMILY H. Historical data on 24 family members were obtained. Eight had a history of bleeding and on examination 6 of these had either an abnormal tourniquet test or a prolonged bleeding time or both. One of the two brothers in generation 1 did not show any laboratory abnormalities when examined in spite of a history of increased bleeding tendency. The symptoms in these 8 subjects consisted of nose bleeds in childhood with a decrease in severity in the second decade of life. Easy bruising, free bleeding after cuts and postoperative hemorrhages were common, but varied in intensity. A more detailed history is provided of the patient studied in detail.

BH (A), is a 29-year-old woman. During childhood she was taken to the doctor frequently because of severe nose bleeds. There also was a marked tendency to bruise and prolonged bleeding after minor cuts. Menstrual periods were very irregular and there was occasional menorrhagia. A first pregnancy at 17 years was characterized by intermittent vaginal bleeding after the fourth month and postpartum hemorrhage occurred with required blood transfusions. A second pregnancy was uncomplicated. At the age of 25 a dilatation and currettage was unsuccessful in controlling menorrhagia and a hysterectomy was performed. At 28 years, intermittent bleeding occurred for one week after extraction of three teeth.

FAMILY J. Of 24 family members, 8 had a history of increased bleeding tendency. The onset was in childhood and the symptoms were prolonged bleeding after cuts, easy bruising, moderate epistaxis, bleeding from the gums and adenoids, and postoperative hemorrhages. Separate histories are provided of the 2 patients studied in detail.

JJ (A), a 15-year-old female, had suffered from nose bleeds once a week since early childhood. These had become less frequent

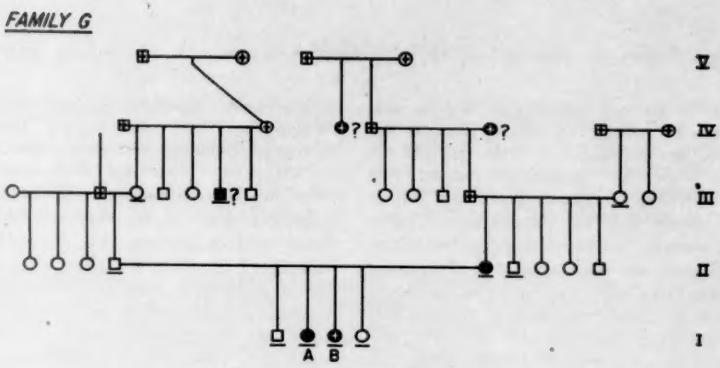

Fig. 1.—Family G.

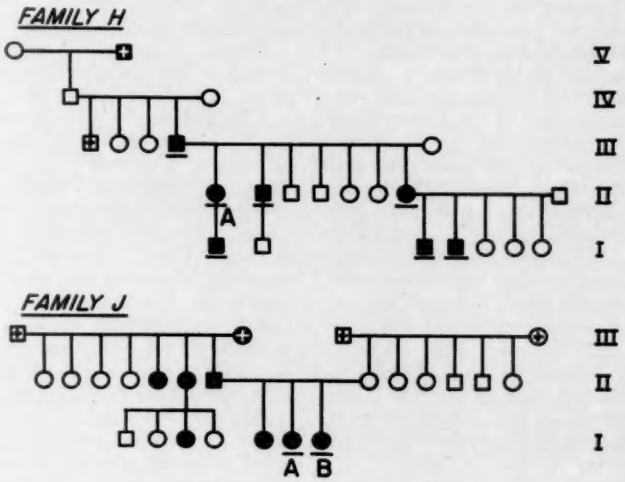

Fig. 2.—Families H and J

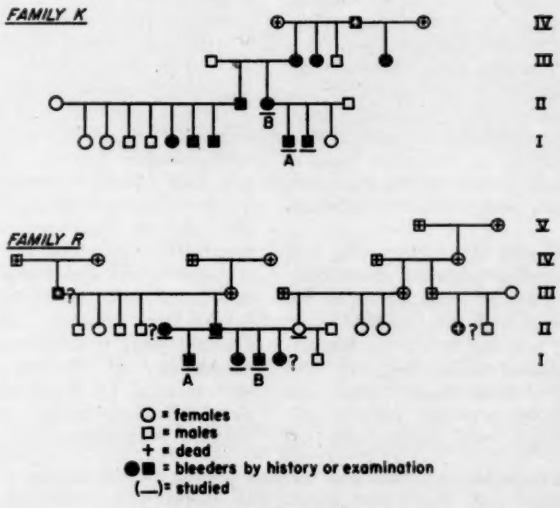

Fig. 3.—Families K and R

and severe with increasing age. There was spontaneous bleeding from the tonsils. At the age of 14, her second menstrual period resulted in extensive bleeding, lasting one week. A decrease in hemoglobin to 50% at this time required blood transfusions. Thereafter her menses remained regular but occasionally blood loss was excessive. Increased bruising tendency after trauma with the target appearance of the bruise was a typical feature. No excessive bleeding was observed following cuts, or with loss of primary teeth.

JeJ (B) is a 17-year-old female with a marked tendency to bruise. The subcutaneous hemorrhages often showed the typical target appearance. On one occasion hemorrhage from a tooth socket followed extraction, continued for days, and was difficult to control. Frequent oozing occurred after dental care. There were no nose bleeds or menorrhagia.

FAMILY K. Historical data on 22 family members were obtained. Of these, 11 had a history of a bleeding disorder. The hemorrhagic manifestations were first noticed in early childhood and include prolonged bleeding from cuts, from tonsils, easy bruising, excessive bleedings after tooth extractions, after tonsillectomy and following delivery. The defect in the hemostatic mechanism was confirmed by routine laboratory tests in the 3 patients it was possible to examine and consisted of a positive tourniquet test and a prolonged bleeding time. In 2 of these, more extensive studies were done and these patients' histories are provided in detail.

KJ (A) is a 7-year-old boy with increased bleeding tendency since early childhood. He had frequent epistaxis after minor trauma, as well as bleeding from the gums and tonsils. Prolonged bleeding occurred with loss of primary dentition and after tooth extraction. He was hospitalized at 7 years of age because of uncontrollable hemorrhage from the tonsils during an episode of tonsillitis. Frequent iron medication was required because of blood loss anemia. There was no prolonged bleeding after cuts, and none after circumcision.

GJ (B) is a 37-year-old woman who had suffered from a bleeding tendency since childhood. There was frequent epistaxis up to the age of 30 occasionally lasting several days and an increased bruising tendency. Repeatedly there was prolonged bleeding from the gums and tooth sockets after dental care and hemorrhage also occurred after tonsillectomy. Menorrhagia was severe and on two occasions hemorrhagic complications after delivery required transfusions. There was no increased bleeding tendency after small cuts.

FAMILY R. Historical data on 31 family members were obtained. Of these, 4 had a definite history of an increased bleeding tendency and on examination showed a positive tourniquet test. The bleeding time was normal but had been markedly prolonged on other occasions. Four had a questionable history of bleeding. Symptoms appeared in early childhood and consisted of epistaxis, easy bruising, prolonged bleeding after lacerations and bleeding episodes after minor surgery. Two patients were studied in detail and their histories are given separately.

IR (A), a 21-year-old man, had a bleeding tendency which was first noted at the age of 5. Weekly nose bleeds occurred which usually lasted several hours and bleeding from small cuts was prolonged. Bruises had a typical target appearance of the hemorrhage. There was prolonged bleeding when the primary teeth were lost and bleeding also occurred after tooth extraction and after tonsillectomy. Gastrointestinal hemorrhage was noted once, lasting one month. Between the ages of 5 and 8, iron medication did not control the anemia and frequent blood transfusions were necessary to combat the blood loss and to stop the bleeding. After the age of 8, there was some decrease in the hemorrhagic manifestations.

TR (B). This 5-year-old boy had suffered from frequent nose bleeds since childhood with a tendency to bruising and profuse and prolonged bleeding after lacerations. Excessive hemorrhage after circumcision had also been troublesome.

Laboratory Data. In all 8 patients studied in detail the Quick prothrombin time (Ham[10]) was within the normal range, thus excluding deficiencies of factor V (proaccelerin, labile factor) and factor VII (proconvertin, stable factor). The thrombin clotting time (Quick[23]) was normal, demonstrating the absence of a circulating antithrombin. The plasma fibrinogen level (Ratnoff and Menzie[25]) was within the normal range. Clot retraction (Ackroyd[1]) was quantitatively normal in all subjects. Platelet counts obtained by a direct counting method (Feissly and Lüdin[8]) were within the normal range. The morphology of platelets was evaluated in each instance by phase microscopy. Sectioned platelets* were studied in 5 cases with the electron microscope. No morphologic abnor-

*Platelets were concentrated from platelet rich plasma by differential centrifugation in the cold centrifuge using siliconized equipment. The blood was decalcified with Sequestrene, using 1 part 1% Sequestrene and 9 parts blood. The thrombocytes were prepared for electron microscopy by techniques described by Kautz and de Marsh[16].

malities were demonstrated in the thrombocytes of the individuals studied by either method. An electron micrograph of sectioned platelets is shown in Fig. 4.* The bleeding time was variable. Moderate to severe prolongations were typically found although it could be normal on a single examination. The tourniquet test was abnormal in all patients. These findings are summarized in Table 1.

Capillary microscopy was performed. The capillaries at the base of the cuticle of the nail bed were examined with a binocular microscope under direct illumination with a green filtered light.† The capillaries in the cases G-A, H-A and K-A had a retiform pattern with many anastomoses and without the regular rows of hairpin loops of the normal individual. In other cases the capillaries appeared quite normal in all respects (R-A, R-B, J-A, J-B).

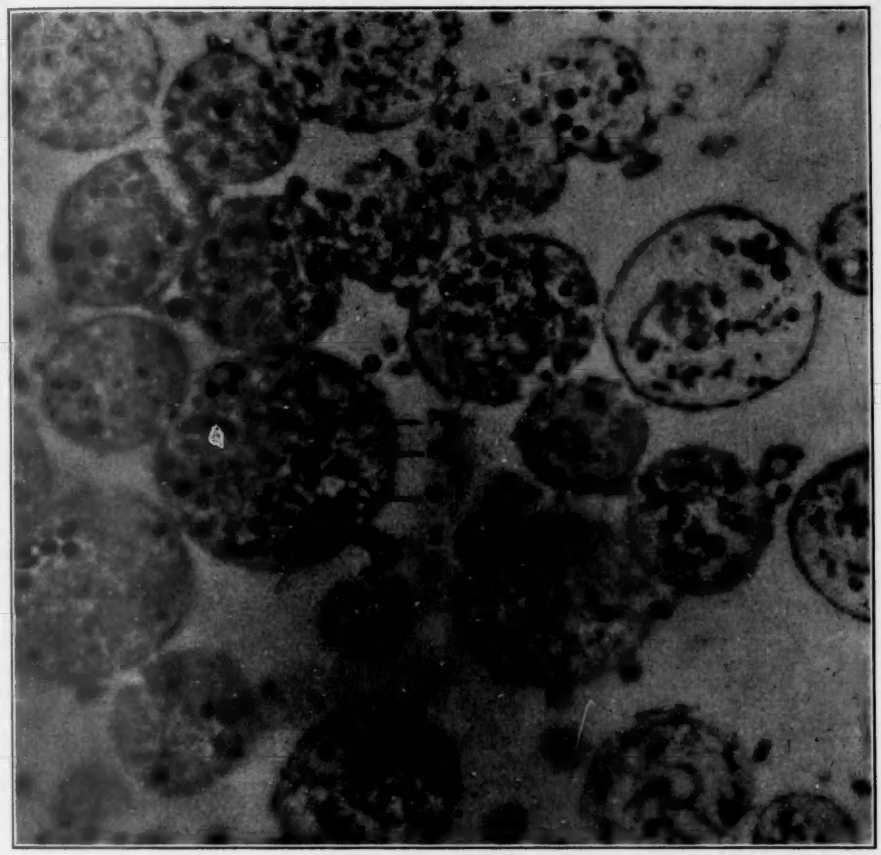

Fig. 4.—Electron micrograph of sectioned platelets from patient JeJ. (PM, platelet membrane; H, hyalomere; G, granules of granulomere; S, spicule.)

Table 2 contains the values for clotting time, recalcification time, and prothrombin consumption in the patients studied. Clotting time was within normal limits or slightly pro-

*Electron microscopy was done in the Department of Anatomy, University of Washington. We are greatly indebted to Miss Jean Kautz who performed these studies.

†The cuticle was prepared by placing a drop of oily cuticle remover (Cutex R) on it for 15 minutes prior to examination.

longed. Recalcification time was normal or slightly lengthened in 4 patients and definitely lengthened in the other 4 patients. The serum prothrombin was measured in plain glass tubes after 2 hours' incubation at room temperature and was found abnormal in 4 cases. The prothrombin content in serum, determined after the incubation of whole blood at room temperature for 24 hours in siliconized tubes, was definitely abnormal in 6 cases. This method (Hill *et al.*[12]) proved to be a sensitive test for establishing the presence of a mild defect. Mixing experiments with as little as 1/10 normal plasma resulted in normalization on the patients' prolonged recalcification time. This excludes a circulating antithromboplastin in these cases.

TABLE 1.—RESULTS OF BLEEDING TIME AND TOURNIQUET TEST

Pedigree	*Patient*	*Bleeding Time in Min. (Duke)*	*Tourniquet Test 90 mm. Hg for 7'*
	Normal range	1:3	− (+)
G	A	16:30	+++
	B*	23:24	−
H	A	2:1½	+++
J	A	3:60	++
	B	3	++
K	A	3:60	+
	B	7:30	+
R	A	2:½	++
	B	1:3½	++

METHODS:
Tourniquet test: Interpretation
− No or < 20 petechiæ/2.5 cm.² below antecubital area
\+ < 20 petechiæ/2.5 cm.² b.a.a.
++ Positive over entire forearm
+++ Loaded with petechiæ
++++ Ecchymoses
(+ results are occasionally found in normal individuals)
* Results taken from hospital chart

To study the generation of thromboplastin in more detail, the thromboplastin generation test (Biggs and Douglas[3]) with the modification of Duckert *et al.*[6] was performed with the following results:

1) The curves obtained after incubating the patients' serum with normal $BaSO_4$ adsorbed plasma and normal platelets were within normal limits. From these observations a deficiency of PTC (hemophilia B factor, Christmas factor) can be excluded.

2) Thrombocytes were tested by incubating the patient's platelets with normal serum and normal $BaSO_4$ adsorbed plasma. The platelets were washed several times, and the test was performed with unagglutinated thrombocytes suspended in 0.9% saline according to the method of Flückiger, Hässig and Koller[9]. Control tests were carried out with suspensions of normal platelets in the same concentration (40,000 to 70,000 platelets per c.mm.) prepared in the same way at the same time. The thromboplastic activity of the platelets was found to be normal in all cases.

3) To test the plasma fraction, the patients' $BaSO_4$ adsorbed plasma was incubated with normal serum and normal platelets. The findings are presented in Fig. 5A. For comparison, the range of normal control determinations simultaneously performed is shown in the shaded area. A definite deficiency in the thromboplastin generation was shown in four of eight curves. The deficiency was severe in one case and relatively mild in the remaining 3. Four other curves were within normal range. Since freezing and thawing of serum in glass may activate PTC (Rapaport, Aas, and Owren[24]) and so mask minor deficiencies of antihemophilic globulin, a further series of tests were done with unfrozen serum. Using this technique, differences between the normals and the patients appeared more pronounced (Fig. 5*B*).

Quantitation of the antihemophilic globulin was performed. In this study, a quantitative method employing the thromboplastin generation test (Duckert *et al.*[6]) was used. All the determinations were done with the same frozen serum and frozen platelets. In this system, the $BaSO_4$ adsorbed plasma fraction of the patients and the normal controls were the only variables. The minimal clotting time was assumed to reflect the content of antihemophilic globulin (Biggs, Eveling and Richard[4]). Serial dilutions of $BaSO_4$ adsorbed plasma from a normal control individual and from each patient were compared to a standard reference plasma. (This assay is basically similar to that described by Biggs[4] in which serial concentrations giving the same clotting time are compared for quantitation.) Values of twenty normal control plasmas varied from 60 to 190% as related to one reference plasma employed in these studies. Patients percentages varied from 3 to 75%. These results are illustrated in Fig. 6.

TABLE 2.—VALUES FOR CLOTTING TIME, RECALCIFICATION TIME AND PROTHROMBIN CONSUMPTION

Method		*Lee-White*[10] *Clotting Time in Min.*	*Recalcification*[10] *Time in Seconds*	*II Stage % Prothrombin Remaining in Serum*[35]	
Normal range		5–12	90/100–120/150*	Plain tubes 2 h. room temp. <10 (24 h. < 5)	Siliconized tubes 24 h. room temp. <30
Pedigree	*Patient*				
G	A	5–10	150/240 220/270	25 9 (24 hr.)	
	B**	7			
H	A	13½	125/135	9	36½ 24
J	A	14½	175/220		37, 15
	B	13½	120/145	25	67
K	A	12	115/140	34	46
	B	12	115/145	36	40
R	A	16	100/120, 150/160	3 (24 hr.)	47
	B	12	150/175		34

* Time: First appearance of fibrin strands/formation of solid clot
** Result taken from hospital chart

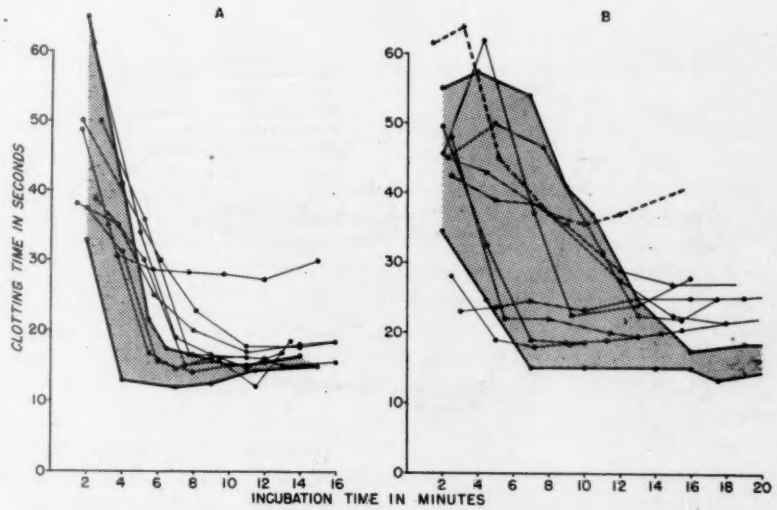

Fig. 5A.—Thrombolastin generation test curves using the $BaSO_4$ adsorbed plasma fraction of the patients. Shaded area-range of controls. *B.* Thromboplastin generation test curves using the patients $BaSO_4$ adsorbed plasma fraction + the serum fraction of either the patients or the controls. Shaded area-range of controls.

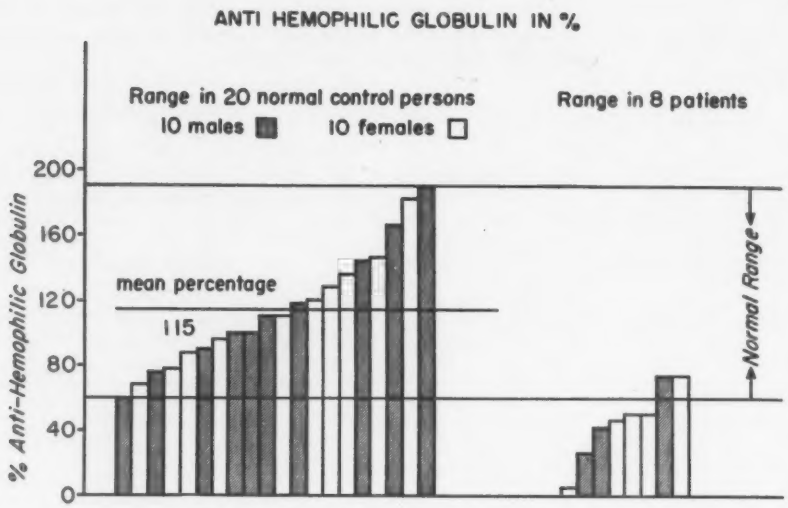

Fig. 6.—The patients from left to right are:
Pedigree:Patient
G:A
R:B
R:A
T:A
T:B
K:B
K:A
H:A

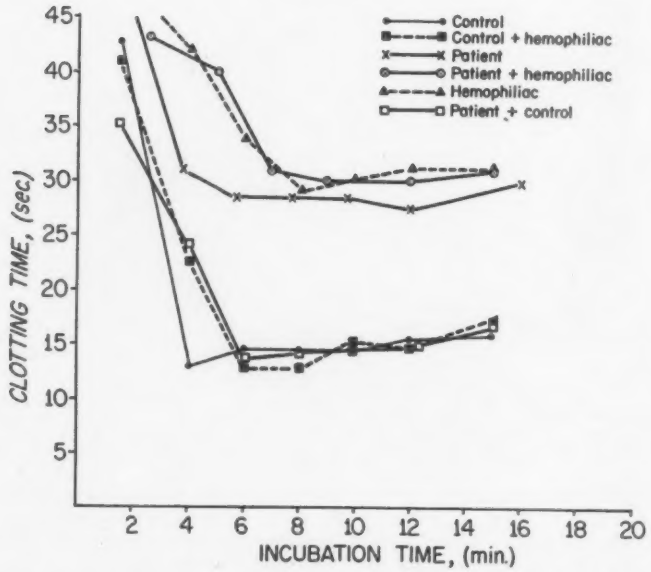

Fig. 7.—Thromboplastin generation test curves using the $BaSO_4$ adsorbed plasma fractions of patient G.G. hemophilia A and normal control. The results of the corresponding 1:1 mixtures of these plasmas are shown.

Patient A pedigree G showed the most pronounced defect in the $BaSO_4$ adsorbed plasma fraction. The antihemophilic globulin concentration was found to be less than 5% with both the quantitative thromboplastin generation test and the partial thromboplastin time (Langdell, Wagner and Brinkhous[17]). Blood and plasma mixing experiments with a known case of hemophilia A (M. T.) were performed, and the data are shown in Table 3. The clotting and recalcification times of this mixture were slightly prolonged. The prothrombin consumption in the mixture was equal to the prothrombin utilization in patient A's serum. When an equal mixture of $BaSO_4$ adsorbed plasma from this patient and from a severe hemophiliac (Hemophilia A) was studied by the thromboplastin generation test, the defect persisted. Results are shown in Fig 7. Normal plasma in the same concentration corrected both patient A's and the hemophilic defect. Quantitative studies of antihemophilic globulin in 8 members of this patient's family, using the technique of the thromboplastin generation test, showed no evidence of a deficiency of this factor. The percentages varied between 70 and 150%, as compared with the reference plasma. Similarly, the bleeding times were normal in the parents and living siblings of this patient. The only abnormality found was a strongly positive tourniquet test in the patient's mother.

TABLE 3.—BLOOD AND PLASMA MIXING EXPERIMENTS WITH A KNOWN CASE OF HEMOPHILIA A

	Lee White Clotting Time in Minutes	*Recalcification Time in Minutes*	*Prothrombin consumption 4 hours room temp. regular glass tubes.* Per cent prothrombin in serum*
G. A.	6	150/240	13
M. T. Patient with hemophilia A	65	300/840	90
G. A./M. T. Mixture 1:1	12½	195/360	13

* Prothrombin content in normal controls $< 5\%$ Methods: See Table 2

Discussion. The clinical characteristics of this hereditary hemorrhagic diathesis have been presented in detail in the introduction. The manifestations and routine laboratory findings of the group of patients studied here are identical to those previously reported.

In considering the pathogenesis of the disorder, previous reports have directed attention towards three possible defects: a vascular lesion, a qualitative platelet defect, and a disturbance of the plasma coagulation mechanism. The prolonged bleeding time and abnormal tourniquet test suggest the presence of a vascular lesion. A disturbance of the capillary morphology was first described in a case of v. Willebrand[33]. This finding was confirmed by Macfarlane[20] who, by microscopic examination of the nail bed, showed distorted and bizarre shaped capillaries which failed to retract promptly after puncture. Similar cases were reported by Imerslund[13], Levy[19], Estren, Sanchez and Damashek[7] and Perkins[21]. The latter two found no abnormal capillary morphology but impaired retraction after puncture. We were able to demonstrate abnormal capillary morphology in 3 of 7 cases studied. It must, therefore, be assumed that a vascular abnormality exists.

A qualitative defect in platelet function could produce vascular as well as coagulation effects. In this regard, Morawitz and Jürgens[34] reported that platelet agglutinability was impaired and thrombus formation delayed as tested by several methods (hanging plasma drop, capillary thrombometer). However, their measurements would not appear specific and might similarly be caused by a deficiency of a plasma coagulation factor since platelet agglu-

tination and thrombus formation are also greatly impaired in hemophilia.

The venous clotting time, while normal in most reported instances, is occasionally slightly prolonged (Jürgens and Forsius[15], Revol, Favre-Gilly and Ollaguier[26] and Schulman *et al.*[28]). In 1951, Jürgens and Forsius[15] found the prothrombin consumption to be abnormal in 6 cases with severe clinical manifestations. Thus, a deficiency in the blood thromboplastin formation was established.

The unsettled question has been whether the coagulation defect resides in the platelets, in a plasma factor, or in both, and whether different patients may possess different defects. Several authors, employing different methods in evaluating this problem, have presented variable results and interpretations. On the basis of abnormal thrombelastograms (Hartert[11]) and deficient platelet function in the thromboplastin generation test (Jürgens[14]), it was concluded that the Aaland-Island cases have a platelet deficiency. That other factors participating in the first phase of coagulation can be decreased in patients with this syndrome was first shown by Alexander and Goldstein[2] who described low levels of antihemophilic globulin in combination with a vascular disturbance in 3 cases. Similar cases have been reported by Larrieu and Soulier[18], v. Creveld *et al.*[32], Schulman *et al.*[28], Darte[5], and Verstraete[31].

Our patients showed a vascular lesion combined with a deficiency of antihemophilic globulin which was demonstrated in the $BaSO_4$ adsorbed plasma fraction by means of the thromboplastin generation test. Further proof that the factor measured is the antihemophilic globulin was obtained in mixing patients' plasma with plasma of a known Hemophilia A. Quantitative determinations of antihemophilic globulin showed that percentages varied from 3 to 75% in the patients as compared to the range of 60 to 190% in the normal control individuals.

In 1953, Rosenthal *et al.*[27] and Spaet *et al.*[29] described a mild defect in the first phase of coagulation in a number of clinically similar hemophilia-like diseases. Rosenthal's cases are of considerable interest in reference to our own data. They are considered to be due to a deficiency of a new coagulation factor, plasma thromboplastin antecedent (PTA). This factor is not consumed during coagulation and is, therefore, present in normal serum. As it is only partially adsorbed on alkaline earth metal salts, it is also present in normal $BaSO_4$ adsorbed plasma. In mixing experiments using serum and $BaSO_4$ adsorbed plasma, the defect can, therefore, only be demonstrated if both fractions are deficient in PTA factor. In our group of patients, however, a defect was demonstrable in the thromboplastin generation test using the $BaSO_4$ adsorbed plasma fraction alone in 4 of 8 patients. Assaying patients' $BaSO_4$ adsorbed plasma with patients' fresh serum in this test, the defect appeared to be more pronounced. This, however, was considered to be related to the difference in PTC activity in fresh as opposed to frozen serum (Rapaport, Aas and Owren[24]), as the same changes in activity were found when fresh normal control serum was assayed.

In all our cases, clot retraction, morphology of the platelets studied by phase and electron microscopy and evaluation of platelet function in the thromboplastin generation test showed no evidence of an abnormality of these elements. The impaired prothrombin consumption is adequately explained by the mild deficiency in antihemophilic globulin.

The question arises whether the defect in antihemophilic globulin found

in our cases plays an important role in the hemorrhagic diathesis observed in these patients. It is of interest that the most severe clinical bleeding disorders were present in those patients with the greatest deficiency of this factor. On the other hand, the severity of the bleeding was disproportionate if explained on the presence of this deficiency alone. In addition, the fact that the prolonged bleeding time is one of the most characteristic findings suggests that the capillary factor must play an important role in the pathogenesis of this bleeding disorder. The combination of a vascular defect with decreased levels of antihemophilic globulin justifies the appropriate designation "vascular hemophilia" for this group, as suggested by Schulman *et al.*[28].

While one accepts with some reluctance a double lesion involving the blood vessels and a coagulation defect, the evidence presented permits no other conclusion. In reference to this combined defect, the observations of Pool and Spaet[22], suggesting that the antihemophilic globulin may be produced by the reticuloendothelial system, are of interest. The speculation of a common denominator between vascular system and antihemophilic globulin gains support if one considers the reticuloendothelial system as a part of the general vascular endothelium.

Analysis of pedigrees with a dominant heredity typical for this disorder shows that a non-sex-linked dominant pattern is followed in most instances[26]. Dominant sex-linked transmission of the gene with location in the x or y chromosome, however, has been described (Revol, Favre-Gilly and Ollaguier[26]).

In families H, J, K and R the hereditary pattern is interpreted as reflecting an autosomal dominant gene with a high penetrance and variable expressivity. The dominance of transmission is shown by an incidence of 50% (31 of 62 individuals) of clinical or laboratory abnormalities, or both, in the descendants. Because of the agreement between the theoretical and actual ratio of affected individuals and the transmission of the gene through consecutive generations without skipping, penetrance must be considered high. The autosomal (as contrasted to sex-linked) transmission is indicated by an equal involvement of males and females (16:15) and by the transmission of the gene from father to son (pedigrees H, K and R). The variation from patient to patient in severity of bleeding illustrates the variable expressivity of the gene.

In family G where a particularly marked deficiency of antihemophilic globulin was found, antihemophilic globulin levels of 8 family members studied were normal. However, the mother had a strongly positive tourniquet test. It seems logical to include the family in this group because of the presence of a vascular component in association with an antihemophilic globulin deficiency in a girl and the lack of the classic genetic pattern of hemophilia.

The fact that the production of antihemophilic globulin may be interfered with by two different genetic mechanisms is of considerable interest. Mild hemophilia A in a male with a decreased level of antihemophilic globulin can, therefore, be differentiated from vascular hemophilia only if a) recessive sex-linked heredity is demonstrable in the family of such an individual, or, b) in a patient with no family history, bleeding time and tests for capillary resistance are normal.

Finally, it is emphasized that our findings do not imply that all cases with a clinically similar bleeding disorder have a combination of a vascular anomaly and a defect in anti-

hemophilic globulin. For example, the data of Jürgens[14] suggest that abnormalities in platelet function may lead to a clinically indistinguishable syndrome. With the development of new and more precise methods, the pathogenesis of these different hemophilia-like diseases should be further clarified.

Summary. The pedigrees of 5 families with a hemorrhagic diathesis are presented. The clinical and routine laboratory findings are compatible with the diagnosis of pseudohemophilia or v. Willebrand's syndrome.

A detailed study of the hemostatic mechanism revealed vascular abnormalities as demonstrated by prolonged bleeding time, increased capillary fragility and changes in capillary morphology. In addition, a defect in the first phase of coagulation was present. By means of the thromboplastin generation test this defect was localized in the antihemophilic globulin fraction. Using quantitative methods, the percentages of antihemophilic globulin in the patients studied ranged from 3 to 75% as compared to 60 to 190% in the control group.

This disorder is designated vascular hemophilia in view of the association of a vascular defect with a deficiency of antihemophilic globulin. The possible etiology of the defect and its role in the pathogenesis of bleeding are discussed. Since the inheritance pattern in 4 of 5 families is that of an autosomal dominant with high penetrance and variable expressivity, it is apparent that antihemophilic globulin deficiency can occur in a disorder genetically different from classic hemophilia (A).

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SUMMARIO IN INTERLINGUA

Hemophilia Vascular: Le Association de un Defecto Vascular con Deficientia de Globulina Antihemophilic

Es presentate le arbores genealogic de 5 familias con diathese hemorrhagic. Le constatationes clinic e le routinari constatationes laboratorial es compatibile con un diagnose de pseudohemophilia o syndrome de v. Willebrand.

Un studio detaliate del mechanismo hemostatic revelava anormalitates vascular que se manifestava in prolongate tempores de sanguination, augmentate fragilitate capillar, e cambiamentos in le morphologia capillar. In plus esseva presente un defecto in le prime phase de coagulation. Per medio del test de generation de thromboplastina iste defecto esseva localisate in le fraction antihemophilic de globulina. Le procentage de globulina hemophilic in le patientes studiate variava inter 3 e 75 in contrasto con procentages de 60 a 190 in le gruppo de controlo.

Le disordine es designate como hemophilia vascular in vista del association de un defecto vascular con un deficientia de globulina antihemophilic. Le possibile etiologia del defecto e su rolo in le pathogenese de sanguination es discutite. Proque le patrono hereditari de 4 inter le 5 familias es illo de un dominante autosomal con alte penetrantia e variabile expressivitate, il es apparente que deficientia de globulina antihemophilic pote occurrer in un disordine que es geneticamente distincte de hemophilia classic.

RELATIVE STABILITY OF PLASMA ANTIHEMOPHILIC FACTOR (AHF) UNDER DIFFERENT CONDITIONS OF STORAGE*

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Hemorrhage in hemophilia is related to a deficiency of a plasma protein, the antihemophilic factor (AHF), needed for clotting and hemostasis. The success of transfusions in the treatment of bleeding in this disease is attributed to the AHF supplied by the transfused blood or plasma. It is frequently desirable to use bank blood or plasma for transfusions rather than freshly collected blood. However, widely divergent results have been reported regarding the effect of storage on the antihemophilic activity of whole blood or plasma. This lack of agreement is shown in Table 1, which lists previous work on this subject. Some of the earlier reports (Alexander[1], van Creveld[10] and Taylor *et al.*[25]) indicated that considerable activity was still observed up to 6 months of storage. Certain later studies (Davidson *et al.*[11] and Spaet and Kinsell[24]), on the other hand, indicated that extensive deterioration of AHF occurred after only 24 hours of storage, and a widespread impression has been created that AHF is rapidly lost in stored blood.

In the past few years, newer knowledge regarding hemophilia and certain hemophilia-like diseases has resulted in better methods for measurement of antihemophilic activity. Prior to 1951, true hemophilia was not differentiated from hemophilioid state C (Christmas disease, PTC deficiency). It is possible that in some of the earlier studies on AHF lability, the blood used as a substrate in testing for antihemophilic activity may not have been obtained from a true hemophiliac, and that some coagulant factor other than AHF was being measured. In 1954, it was shown that an accelerator factor or factors which develop in serum and perhaps in stored blood as well affect AHF assay procedures. The serum factor appears to act synergistically with AHF to give false high values in *in vitro* test procedures (Graham *et al.*[14]). It has also been shown that remarkably small amounts of AHF are sufficient to cause the delayed whole blood clotting time or impaired prothrombin utilization of hemophilic blood to become normal[6]. If such tests are used, great differences in concentration of AHF may be undetected.

A restudy has been made of AHF in preserved blood and plasma, using an assay procedure both specific and sensitive for this clotting factor. The influ-

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Date	Authors	Test Procedure*	Material**	Storage Temperature (C.)	AH Activity
1936	Patek and Stetson[19]	*In vivo* (1) and *in vitro* (2)	Citrated blood Citrated plasma	5–10° 5–10°	No loss in 3 days "Stable at ice-box temperature"

Date	Authors	Test Procedure*	Material**	Storage Temperature (C.)	AH Activity
1936	Patek and Stetson[19]	*In vivo* (1) and *in vitro* (2)	Citrated blood	5–10°	No loss in 3 days
			Citrated plasma	5–10°	"Stable at ice-box temperature"
1937	Patek and Taylor[20]	*In vitro* (2)	Citrated plasma	46°	Complete loss in 16 hours
			Citrated plasma	43°	Complete loss in 48 hours
			Citrated plasma	37°	Partial loss in 48 hours
			Citrated plasma	5°, 10°, 24°	No change in 16 to 48 hours
1940	van Creveld[10]	*In vitro* (3)	Citrated blood	4°	Active for 37 days
			Citrated plasma	4°	Variable activity to 4 months
1942	Johnson[16]	*In vivo* (1)	Citrated plasma, freshly lyophilized	5°	Stable for 90 days
			Citrated plasma, lyophilized after 7 and 21 days	5°	Loss in potency
1944	Taylor *et al.*[25]	*In vitro* (2)	Citrated pooled plasma	30°, room	Full potency after 6 months
1947	Alexander[1]	*In vivo* (1) *and in vitro* (3)	Plasma	Frozen	No loss for 6 months
			Plasma	5°	50 to 90% loss in 5 to 10 weeks
			Plasma	37°	50 to 85% loss in 10 to 24 hours
1949	Graham *et al.*[13]	*In vivo* (4)	Citrated blood and plasma (canine)	28°	Partial loss in 24 hours
1949	Davidson *et al.*[11]	*In vivo* (1)	Plasma	Refrigerator	Advise against use of liquid plasma over 24 hours old as source of AH activity
1950	Marotta *et al.*[18]	*In vivo* (1) and *in vitro* (2)	Formalin-treated plasma	Room	No loss in 1 week; complete loss in 2 years
1953	Biggs and Macfarlane[5]	?	Blood, plasma	4°	"Unpredictably labile"; some activity to 14 days
1953	Pitney and Dacie[22]	*In vitro* (5)	Citrated plasma	−20°	Potent after 10 days
			Citrated plasma	4°	Half as potent as above in 10 days
1953	Spaet and Kinsell[24]	*In vitro* (7)	Human plasma	4° and 20°	50% loss in 1 day
			Bovine, porcine, ovine plasma	4° and 20°	Stable
1954	Penick and Brinkhous[21]	*In vitro* (6)	Citrated plasma (canine, human)	−20°	Active for several months
			Citrated blood (canine, human)	4°	Active for weeks
			Citrated plasma	28°, 37°	Loss of activity, but more stable than in oxalate
1955	Spaet and Garner[23]	*In vitro* (7)	Citrated plasma	4°	Activity maintained for 40 days
			Oxalated plasma	4°	Labile in 1 to 7 days
1956	Brinkhous *et al.*[8]	*In vitro* (6)	Citrated plasma	−20°	Partially active at 1 month
			Citrated blood	4°	Partially active at 1 month
			Lyophilized plasma	4°	About 50% activity; stable

* Test Procedure: (1) Whole blood clotting time (WBCT) after transfusion of stored material to hemophilic (H) patient.
(2) WBCT of H blood after addition of stored material.
(3) WBCT of H blood after additions of serially diluted stored material.
(4) WBCT and prothrombin utilization after transfusion of stored material to H dogs.
(5) Thrombin generation of H plasma after addition of diluted stored material.
(6) AHF assays.[17]
(7) Prothrombin time of serum from H blood after addition of stored material.

** Human plasma or blood unless otherwise indicated.

ence of different storage conditions on the lability of AHF has been investigated also. Preliminiary data from this study were reported earlier[8,21].

Materials and Methods. Human bank blood used in the storage experiments was prepared by drawing 380 ml. blood from healthy donors into 120 ml. acid-citrate-dextrose (ACD) solution, U.S.P., using commercial donor sets (Abbott or Cutter Laboratories). The ACD solution contained 2.45% dextrose, 2.2% sodium citrate and 0.8% citric acid. Storage temperature was 4° C. Lyophilized pooled human plasma (Hyland Laboratories) had been subjected to ultraviolet irradiation prior to lyophilization. About 25 to 30 donors contributed to each plasma pool. The dried plasma was reconstituted to original volume as instructed by the manufacturers with water containing 0.1% citric acid, U.S.P.

Citrated or oxalated plasmas were prepared by drawing 7 parts blood into one part anticoagulant (0.109 M sodium citrate or 0.1 M sodium oxalate); sterile precautions were observed. Native platelet-poor plasma was prepared by a method previously described[9]; sodium oxalate solution was added in the proportions of one part to 5 parts plasma. Resin-treated plasma was prepared from blood drawn into siliconed syringes and immediately transferred to a resin column. One milliliter wet Amberlite IRC–50, sodium cycle (Rohm & Haas Co.) was used for each 5 ml. whole blood to be decalcified. The entire procedure was performed at 4° C.

AHF was determined by the method of Langdell, Wagner and Brinkhous[17]. Prior to assay, plasmas were adsorbed with 100 mg. $BaSO_4$ (Merck) per ml. Before adsorption citrated and resin-treated plasmas were dialyzed with continuous agitation for 2 hours at 4° C. against a solution consisting of 4 parts 0.154 M sodium chloride and one part 0.1 M sodium oxalate. Homologous hemophilic plasma (canine[13] or human) was used in each assay. A single subject with classical hemophilia was the source of the human plasma substrate. Plasma AHF was expressed in per cent, using a freshly collected normal plasma as 100% AHF. In the case of human plasmas, one of us (GDP) furnished the normal plasma control throughout; earlier studies indicated that this plasma contained 72% as much AHF as the mean of 28 normal individuals[17]. Prothrombin was determined by a modified two-stage procedure[26].

Results. AHF IN STORED HUMAN BLOOD. In several preliminary studies, AHF was determined in bank blood at varying periods after storage. Wide variations in AHF activity were observed, even for bloods stored for the same length of time. In general, however, the AHF values were progressively lower as storage time increased. In one set of observations, 70% AHF remained at the end of one week of storage, 27% at the end of one month[8]. In another set of observations, bank blood from 7 donors was stored for a longer period. After 5 to 7 weeks, AHF values of 26 to 64% were obtained. One sample 7 weeks old contained 51% AHF. From these data, it appeared that the decay of AHF was an exponential function of time, with a variable but progressive loss of AHF occurring during the first 3 weeks of storage, and a less rapid decline thereafter.

Previous work has shown that plasma AHF values of normal individuals vary widely, ranging from about 60 to 175% of the mean (Biggs, Eveling and Richards[4] and Langdell, Wagner and Brinkhous[17]). A study was made to determine if the variations observed in bank blood were the result of differences in the original AHF levels of the donors. Results are shown in Table 2. Despite the narrow range of initial values (100% to 119%) considerable differences in the AHF remaining after varying periods of storage were observed. This would suggest that factors other than the initial donor level of AHF are important determinants of the amount of AHF remaining after storage.

STORAGE TEMPERATURE AND AHF LABILITY. A study was made of the effect of temperatures in the range of 56° C. to —20° C. Human and canine citrated plasmas were used. Earlier work (Table 1) indicated that AHF is unstable if blood is kept at 37° or higher for 1 to 2 days. On the other hand, it has been shown[15] that AHF is more

heat stable than fibrinogen; at 53° C., the fibrinogen is inactivated while AHF activity still remains. Table 3 shows the data from one experiment on fresh plasma kept at 56° C. for short intervals before testing for AHF. Nearly half of the AHF was lost in 10 minutes, and very little activity was retained in one-half hour.

Table 4 shows the results of one experiment on plasmas stored for 2 weeks at different temperatures. Best preservation of AHF was obtained with the lowest temperature. Other data, not shown in the Table, indicated that with longer storage periods at each temperature, less AHF was preserved. But even after 14 months of storage, the frozen plasma still contained 60% activity.

TABLE 2.—STABILITY OF AHF IN BANK BLOOD STORED AT 4° C.

Storage Period, Weeks	*Per Cent AHF*			
	Donor 1	*Donor 2*	*Donor 3*	*Mean*
0	100	113	119	111
1	56	..	108	82
2	67	56	..	62
3	34	55	33	41
4	43	16	27	29

TABLE 3.—AHF CONTENT OF CANINE CITRATED PLASMA MAINTAINED AT 56° C. FOR DIFFERENT PERIODS OF TIME

Time in minutes.....	0	10	20	30
AHF (per cent).....	100	53	19	11

TABLE 4.—AHF CONTENT OF CANINE CITRATED PLASMA STORED FOR 2 WEEKS AT DIFFERENT TEMPERATURES*

Storage temperatures (° C.).....	—20	4	28	37
AHF (per cent).....	135	79	62	35

* Plasma from single donor, divided into 4 aliquots of approximately 10 ml., was stored at temperatures indicated. Freshly collected plasma from the same donor 2 weeks later was given value of 100 %.

TABLE 5.—STABILITY OF AHF IN FROZEN HUMAN CITRATED PLASMA STORED AT —20° C.*

Storage Period, Weeks	*Per Cent AHF*				
	Donor 1	*Donor 2*	*Donor 3*	*Donor 4*	*Mean*
0	100	113	119	100	108
1	71	70	81	91	78
2	66	79	58	..	68
3	53	62	40	121	69
4	..	21	63	78	54
9	51	..	..	..	..
18	..	..	..	48	..

* Three of four donors same as indicated in Table 2.

Table 5 shows the changes in AHF which occurred in freshly collected human citrated plasma stored in the frozen state. It will be noted that, as in bank blood, a variable and progressive loss in AHF occurred. Plasma from

3 other donors, not shown in the Table, was stored for 7 months at —20° C. The AHF values at that time were 39, 45 and 47%, respectively. It appears that the AHF remaining in frozen plasma after a month of storage is maintained with little additional deterioration for long periods.

The effect of storage at room temperature on AHF was tested on 6 specimens of pooled human plasma. The plasma had been stored for 3 and 4 months, and for 1, 4, 5 and 8 years respectively. Only the sample stored for 3 months showed activity (44% AHF). Its plasma prothrombin was 30% of normal. The 4-month old pool contained 6% prothrombin but no detectable AHF.

DECALCIFICATION PROCEDURE AND AHF STABILITY. Two general groups of studies were made on both human and canine plasmas. In one group, oxalate or resin was used as a decalcifying agent and the stability of AHF on storage of these plasmas was compared with stored citrated plasmas. In the other group of studies, there was a lag period in effecting decalcification. The influence of this delayed decalcification on AHF stability was studied.

It was found that in oxalated plasma, in contrast to resin-treated and citrated plasmas, the AHF was very labile. This difference in AHF stability in stored oxalated and citrated plasma is illustrated in the following experiment. Four sterile samples of oxalated canine plasma and two samples of citrated plasma were kept at 37° C. and the AHF determined repeatedly for 11 days. The time required for the AHF to fall to 15% was 2, 8, 10 and 11 days, respectively, in the oxalated plasmas, whereas in the citrated plasmas the AHF was still at about the 60% level at the end of the experiment. In one group of studies with resin-treated plasma, AHF was maintained at high levels comparable to those in stored citrated plasmas. Frozen human resin-treated plasma, stored at —20° C. for 3 weeks, had 90% AHF. Similar results were obtained with canine plasma.

In the course of collection and testing of blood for AHF, it was noted that even slight delays in the mixing of the drawn blood with the ACD anticoagulant were followed by relatively rapid loss of AHF on storage. This impres-

TABLE 6.—AHF IN POOLED HUMAN PLASMA AT DIFFERENT PERIODS AFTER LYOPHILIZATION*

Weeks after lyophilization	3	4	5	7	7	76	260
AHF in per cent	53	48	51	53	56	42	44

* Stored in refrigerator (about 4° C.) after lyophilization.

AHF IN LYOPHILIZED PLASMA. The AHF in irradiated lyophilized human plasma was tested in a number of samples which had been prepared from 3 weeks to 5 years previously. The results are given in Table 6. There is little difference in the AHF content of the samples, regardless of the length of storage period after lyophilization. All contained approximately 50% AHF. In another experiment a plasma pool was tested before and after both ultraviolet irradiation and lyophilization. There was minimal loss (11%) of AHF following irradiation alone. After lyophilization, the reconstituted plasma showed a loss of 42%. It thus is evident that some AHF is lost after irradiation as well as during the lyophilization-reconstitution process, but that which remains in the dried plasma is remarkably stable.

sion was tested in two experiments, one on human plasma, the other on canine plasma. In one experiment, blood from a human donor was drawn into the bottle and slowly mixed with ACD solution. It was compared with a sample from the same donor which had been promptly decalcified by drawing the blood directly into a 10 ml. syringe containing the ACD anticoagulant. Both samples were stored at 4° C. and tested for AHF. After 24 hours of storage, the blood from the regular collection contained 28% AHF, the syringe sample 84%. After 6 days of storage, <5% AHF was present in the regular collection compared to 60% AHF in the syringe sample. In the other experiment, native platelet-poor canine plasma was prepared[9]. This plasma began to clot in one hour. The anticoagulant was added periodically to aliquots prior to and during the early phases of clotting, and the AHF determined immediately and after 24 hours of storage. The results are shown in Table 7. If decalcification was done prior to clotting, the AHF level remained high. Thereafter, it was observed that the greater the delay in decalcification, the lower the initial AHF value, and the greater the deterioration during subsequent storage.

TABLE 7.—LOSS OF AHF IN CANINE PLATELET-POOR PLASMA* WITH DELAYED DECALCIFICATION AND AFTER 24 HOURS STORAGE AT 28° C.

Time Elapsing Before Adding Anticoagulant, Minutes	*Per Cent AHF*	
	Immediate	*After 24-Hour Storage*
0	100	94
55	78	84
60**	66	37
75	39	11
80	18	<5

* Blood collected at 4° C. without anticoagulant and handled in silicone-treated equipment throughout preparation. Time lapse between transfer of native plasma to glass tubes and addition of anticoagulant is indicated in Column 1.

** First fibrin strands observed immediately prior to this time. Delicate flimsy clot had formed at 80 minutes.

Discussion. Our studies of AHF in preserved blood or plasma are in accord with certain previous observations regarding the variable lability of this clotting factor. The finding of a high AHF content in many stored preparations suggested that, with proper circumstances of collection and preservation, AHF can be stabilized. In general, AHF deteriorated fastest during the first 1 to 3 weeks of storage, and thereafter it tended to be more stable.

Temperature of storage appears to be a significant but not necessarily crucial factor. Stability was greatest at the lowest temperature. In the frozen state nearly complete preservatioin was observed at times during the first few weeks of storage. As a rule, however, roughly half of the antihemophilic activity disappeared in a month, after which time there was little further loss over the next several weeks. Rapid inactivation occurred at the highest temperature tested (56° C.). Lyophilized plasma showed the most consistent stability of AHF of all the preparations tested. It was relatively stable for 5 years of storage.

The AHF in human plasma is less stable than in animal plasma. In all of our comparative studies with human and canine plasmas, the canine AHF

was found to be more stable. AHF in bovine, porcine and ovine plasmas has also been shown to be more stable than in human plasma (Spaet and Kinsell[24]). One is at a further disadvantage in dealing with human plasmas, since they possess relatively low AHF activity. Human plasma contains at the most only 20% as much AHF as canine, porcine or bovine plasmas (Bidwell[3] and Brinkhous, Morrison and Muhrer[7]).

A full explanation of the variability in AHF in stored blood has not yet been obtained. An original high level of AHF in the donor blood, while important, did not in itself insure a high level of AHF after storage (Table 2). Some factor in the collection or preservation of the blood, or some other factor in the blood itself must be uncontrolled. An important consideration appears to be rapid decalcification of the plasma. We have shown previously[15] that AHF is lost during the clotting of blood, and our present findings would indicate that there is some loss at the time clotting is initiated (Table 7). The AHF in both citrated and resin-treated plasmas was often remarkably stable if the blood was carefully collected and promptly mixed with the anticoagulant. Even if the blood were collected meticulously, poor preservation was observed in oxalated plasmas. This finding is in accord with data previously reported (Penick and Brinkhous[21] and Spaet and Garner[23]) and is similar to that observed regarding the increased lability of AcG (labile factor, Factor V) in oxalated plasmas (Fahey, Ware and Seegers[12]).

Natural inactivators of AHF may play a role in the loss of AHF on storage. It was observed several years ago that AHF and prothrombin were lost concomitantly during clotting[15] and it has been suggested that a prothrombin derivative, thrombin, may inactivate AHF (Alexander *et al.*[2]). Since our data would suggest that the earliest phases of clotting are not completely prevented by the usual blood collection technique, it is possible that traces of thrombin are responsible for the instability of AHF on storage. It has been demonstrated that fibrinolysin causes rapid loss of activity in potent AHF fractions[27], and this factor too may be activated in sufficient amounts during collection and storage of blood to cause loss of AHF. Also, it has been postulated that a dialyzable plasma factor exists which specifically inactivates AHF (Spaet and Garner[23]).

Our data indicate that blood or plasma, if carefully collected and preserved, will furnish a good source of AHF for transfusion treatment of hemophilia during the first several days or weeks of storage. Recently drawn blood is preferable to that stored for longer periods, but there appears to be no need to use blood only a few hours old, as is sometimes suggested. Freezing or lyophilization would seem to be the best of the currently available methods for long-term storage of an active plasma. Even these preparations may not have a full complement of AHF, but usually they compare favorably with fresh plasma from subjects whose AHF level is at the lower limit of the normal range.

Summary and Conclusions. 1. Antihemophilic factor (AHF) activity in bank blood and plasma shows variable stability. Deterioration of AHF on storage tends to be slow but progressive, with about 30 to 60% of the initial AHF remaining after a 3-week storage period.

2. Several factors appear to determine the amount of AHF remaining in stored blood or plasma. Studied were the effects of initial plasma AHF level of the donor, care in collection of blood, various types of anticoagulants and the conditions of storage.

3. The lower the temperature of storage, the better the preservation of AHF. In fresh frozen plasma variable stability of AHF was observed; about half is lost in one month, after which time the remaining AHF tends to be stable. At 56° C. the AHF is rapidly inactivated.

4. AHF in lyophilized plasma is remarkably stable for a period of years. Its potency is about half that of fresh plasma following reconstitution.

5. Nearly normal AHF levels were maintained in frozen plasmas which were carefully collected, using either citrate or cation exchange resin as an anticoagulant. AHF is unstable in oxalated plasmas.

6. Possible mechanisms of inactivation of AHF in stored plasma are discussed. For the stabilization of AHF, prevention of the earliest clotting sequences appears essential.

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SUMMARIO IN INTERLINGUA

Stabilitate Relative del Factor Antihemophilic (AHF) del Plasma sub Differente Conditiones de Immagasinage

1. Le activitate del factor antihemophilic (AHF) in sanguine o plasma ab bancas monstra variabile grados de stabilitate. Le deterioration de AHF per immagasinage es lente sed progressive. Circa 30 a 60 pro cento del AHF initial remane presente post un periodo de 3 septimanas de immagasinage.

2. Plure factores pare determinar le quantitate de AHF que persiste in sanguine o plasma immagasinate. Esseva studiate le effectos del concentration initial de AHF in le sanguine del donator, del precautiones prendite in le collection del sanguine, del uso de varie typos de anticoagulante, e del conditiones del immagasinage.

3. Quanto plus basse le temperatura del immagasinage, tanto plus bon le preservation de AHF. In plasmas frigorificate in stato fresc, variabile grados de stabilitate de AHF esseva observate. Circa un medietate se perde in le curso de un mense. Postea le remanente AHF se monstra plus o minus stabile. Al temperatura de 56 C, AHF es rapidemente inactivate.

4. In plasma lyophilisate, AHF es remarcabilemente stabile e remane stabile durante periodos de plure annos. Post reconstitution, su potentia es circa 50 pro cento del potentia de plasma fresc.

5. Nivellos quasi normal de AHF esseva mantenite in refrigerate plasmas de collection meticulose quando citrato o resina a excambio de cation esseva usate como anticoagulante. Le AHF de plasmas oxalate es instabile.

6. Mechanismos possibile del inactivation de AHF in plasma immagasinate es discutite. Le prevention del primissime phases de coagulation es apparentemente essential in le stabilisation de AHF.

THE THYROID PROFILE

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The definitive diagnosis of thyroid dysfunction has been facilitated by the development of new and specific methods of study. Occasionally these tests appear to be inconsistent with the clinical picture and under those circumstances there is a tendency to deprecate their reliability. Whereas it is true that technical errors may yield misleading values, more commonly a discrepancy between the actual and the expected is based upon sound physiologic principles which, if correctly understood and interpreted, reveal to the clinician a clear picture of the type of disorder. Each test measures a different parameter of function and a battery of studies may be required to resolve the diagnostic dilemma. The purpose of this communication is to describe the better known procedures employed in the evaluation of thyroid function and to show how one may reconcile apparently inconsistent laboratory values. To do this, it is necessary to understand the steps by which circulating thyroid hormone is synthesized from serum iodide as well as thyroid-pituitary gland interrelationships.

Ingested iodine quickly finds its way into the blood stream and thence to the thyroid gland where it is trapped in the form of iodide. The trapped iodide may be excreted back into the blood stream unused or it may be transported through the steps of synthesis, eventually contributing to the structure of the thyroid hormone molecule (Fig. 1). Iodide in the trapping compartment may be washed out of the thyroid gland with substances like thiocyanate but once the synthesis of thyroxin has begun this is perhaps no longer possible. Such drugs, when used for long periods of time, as in the treatment of hypertension, may produce hypothyroidism because an insufficient amount of iodine is made available for normal thyroid hormone synthesis by reason of the thiocyanate block. When the level of circulating thyroid hormone is reduced, the brake on the anterior pituitary gland production of thyroid-stimulating hormone (TSH) is released allowing an outpouring of this thyrotrophic substance. The thyroid gland responds to the stimulation by becoming large and hyperplastic resulting in the anomaly of hyperplasia of the thyroid gland but with decreased function.

Normally, trapped iodine is oxidized by a peroxidase enzyme system to molecular iodine which is quickly bound to tyrosine, first to form monoiodotyrosine and then diiodotyrosine with two molecules of the latter condensing to form thyroxin. Antithyroid agents of the thiouracil type depress the peroxidase enzyme system and prevent the liberation of molecular iodine from iodide so that once again insufficient iodine is available and thyroid hormone is formed in inadequate amounts, and the same sequence of events occurs as was described with thiocyanate. However, in this case the trapping mechanism is not affected early and it may continue to pick up large amounts of administered iodine for long periods of

time even though this iodine is subsequently excreted into the blood stream unused. Generally, the trapping mechanism eventually loses its ability to pick up large amounts of iodine.

Synthesized thyroxin is stored in the colloid as thyroglobulin, a large molecule which is not permeable through the capillary walls and which must be broken down to a smaller size. This is accomplished by means of a proteolytic enzyme system within the substance of the colloid. The thyroxin which is so liberated circulates in the serum joined to protein as protein-bound iodine (PBI). This proteolytic enzyme system is under the control of the thyrotrophic hormone of the anterior pituitary gland which, in turn, is regulated by the level of circulating thyroxin. Administered iodine, as in the form of Lugol's solution, blocks the pituitary production of TSH and the uptake of further iodine by the thyroid gland as well as inhibiting the action of the proteolytic enzyme. This explains not only the beneficial symptomatic effect of iodine in thyrotoxicosis but also the reduction in gland size.

It is apparent, then, that there are several separate functions of the thyroid gland which may be evaluated. One may assess the manner in which the gland traps iodine. For example, if a dose of radioiodine is administered and the amount which is retained by the thyroid gland at 24 hours is recorded, the per cent of retention is generally commensurate with the degree of hyperplasia and function. In our laboratory, normal values fall between 15 and 40% with most hypothyroid patients retaining below 10% and most hyperthyroid individuals over 45%. One may also determine the amount of radioiodine which has been converted to serum radioactive hormone (PBI–131) at 24 hours. The conversion ratio (Clark,

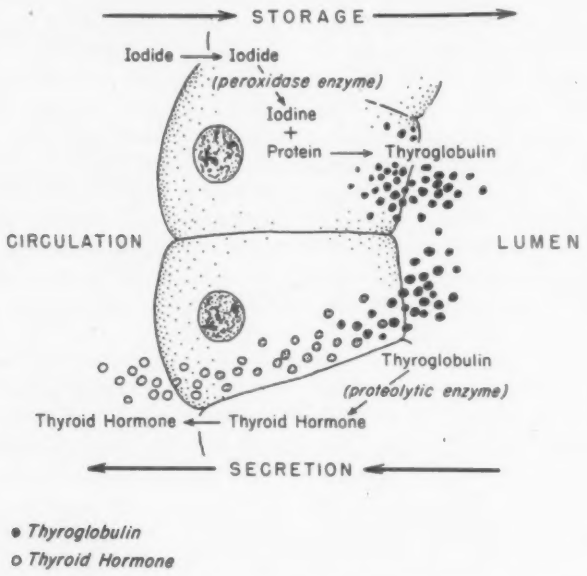

Fig. 1.—Diagrammatic illustration of thyroid hormone synthesis.

Moe and Adams[2]) expressed as $\frac{\text{Protein-bound I–131}}{\text{Total plasma I–131}} \times 100$, is a good index of thyroid hormone release and is usually consistent with the clinical status of the patient. It is generally quite low in hypothyroid individuals (0 to 5%) and elevated in hyperthyroidism (over 50%). Some observers believe that the conversion ratio is the most revealing index of thyroid gland function but, as will be shown later, this test, too, may be grossly misleading.

Whereas the level of circulating protein-bound (nonradioactive) iodine (Brown, Reingold and Samson[1]) is usually an extremely accurate measure of the clinical status of the patient, it is by no means the end and all of diagnosis that so many clinicians believe it to be. It is elevated not only in hyperthyroidism, but unfortunately also in pregnancy, in women receiving estrogen and in patients given iodine or thyroid. Furthermore, it may be lowered as the result of mercurial diuretics. The range of normal serum levels is between 4 and 7.5 micrograms % with below 3.5 representing hypothyroidism and above 8 micrograms % indicating hyperthyroidism. It must be emphasized, as with any biologic phenomenon, that a certain percentage of normal individuals will be expected to fall outside the so-called "normal" range.

The third general method of investigation entails the estimation of the peripheral impact of the thyroid hormone. The basal metabolic rate (BMR) is the best known of all thyroid function studies and the one with which clinicians have had the most experience. It is quite reliable in the definition of both the hyperthyroid and hypothyroid states but, unfortunately, in the euthyroid group where diagnostic difficulties are most frustrating, it is often undependable. The BMR measures oxygen consumption so that metabolic influences other than thyroid activity are uniformly recorded. In fact, it has been estimated that thyroid gland function contributes only approximately 40% to the metabolic rate. Normal values have been accepted generally as minus 15% to plus 15% with a mean at 0, but recent evidence would indicate that healthy young adults are prone to show lower mean values. This whole question deserves reassessment. As has been recognized for many years, the basal metabolism is elevated by fever, anxiety states, hypertension, congestive heart failure, pulmonary insufficiency, blood dyscrasias, acromegaly, thyrotoxicosis factitia and technical errors, and may be lowered by starvation states, obesity, nephrosis, anemia, Addison's disease, Simmonds' disease, eunuchism and faults in the apparatus or technique.

A much maligned and misunderstood test which nevertheless has real value when carefully employed and interpreted is the serum cholesterol. Early observers noted the frequency with which serum cholesterol levels were elevated in hypothyroidism and depressed in hyperthyroidism but, with the usual human tendency to absolutism, subsequent investigators, who found elevations of cholesterol in diabetes, nephrosis, idiopathic hypercholesterolemia, obesity and other nonthyroid disorders, and the marked overlaps which occurred with normals, were inclined to disregard this test and to minimize its importance in the evaluation of thyroid function. It must be admitted that the serum cholesterol is not in itself a definitive procedure to be relied upon implicitly but, when intelligently employed, particularly as regards changes incident to therapy, it is a valuable diagnostic aid. For example, the fall of serum cholesterol from 270 mg. to 200 mg. per 100 ml. induced by desiccated thyroid is in our experience

diagnostic of hypothyroidism whereas the level of 270 mg. per 100 ml. itself is not necessarily so.

In order to compare the relative reliability of each of these procedures (excepting the conversion ratio) 100 patients were evaluated, 60 with normal thyroid function and 20 each with obvious thyrotoxicosis and hypothyroidism. The BMR was above plus 15% in all but one patient with hyperthyroidism, below minus 15% to plus 15% in *only* one-half of the normal group. The serum cholesterol was below 180 mg. per 100 ml. in one-half of the hyperthyroid individuals, above 250 mg. in all but one of the patients with hypothyroidism and within this range in 80% of the normals. The 24-hour I–131 tracer test gave values above 45% in 90% of the thyrotoxic patients, below 15% in 80% of the individuals with hypothyroidism and within this range in 80% of the normals. Serum protein-bound iodine levels were above 7.5 micrograms % in 80% of hyperthyroid subjects, below 4 micrograms % in 75% of hypothyroid patients and within the range of 4 to 7.5 micrograms % in 80% of normals. Radioiodine tracer tests and serum protein-bound iodine levels were 85% accurate in this series in contrast to the BMR and serum cholesterol which were only 60% reliable. This difference in accuracy would be even more marked if the false values of I–131 uptake and serum PBI incident to the previous ingestion of iodine in the form of medication or radiopaque dyes were excluded from the calculations. The BMR proved to be equally as valuable in the diagnosis of hyperthyroidism but much less reliable in patients with normal or decreased thyroid function. Whereas no one laboratory test was invariably dependable, a combination of two or more procedures was consistent with the correct diagnosis in all but 3 patients.

In order to illustrate the manner in which these studies may be employed diagnostically, hypothetical examples will be presented. The data will include symptomatology, BMR and serum cholesterol levels which represent the impact of the thyroid hormone peripherally, thyroid gland size which is generally commensurate with the degree of hyperplasia, the 24-hour thyroid I-131 uptake study which is a measurement of the trapping ability of the gland, the 24-hour serum I–131 conversion ratio which indicates the thyroid gland secretory power and the level of circulating PBI which results from the equilibrium established between thyroid hormone production and release by the gland and peripheral utilization and disappearance. In the accompanying chart (Table 1) a minus sign indicates symptoms of hypothyroidism or test values below the normal range whereas a plus sign represents symptoms of hyperthyroidism or levels above normal. N stands for normal and nod. means nodule.

PATIENT 1 illustrates the findings in an untreated euthyroid individual. There are no symptoms relating to the thyroid, and gland size is normal. There is enough circulating thyroid hormone so that the peripheral metabolic effect is adequate as evidenced by the BMR and cholesterol. The normal values for thyroid I–131 uptake and serum conversion ratio indicate that the gland is trapping and retaining an adequate amount of radioiodine from the serum and converting it to radiohormone in the usual fashion. And, finally, the normal serum PBI indicates that the amount of iodine bound to protein, an inferential measure of circulating thyroid hormone, is normal.

PATIENT 2. Let us now examine the findings in a patient who has been ingesting a diet moderately low in iodine (Stanbury *et al.*[6]). The inadequate dietary iodine leads to a lowered level of serum iodide available to the thyroid gland. Consequently, the amount of thyroid hormone which is produced and which circulates in the blood stream is low, and the anterior lobe of the pituitary gland is allowed to produce more thyrotropic hor-

mone in an attempt to compensate for this deficiency. As a result the gland becomes enlarged and hyperplastic. Under these circumstances a sufficiency of thyroid hormone is produced; the patient is euthyroid, there are no symptoms and there is enough circulating thyroid hormone as evidenced by the BMR, cholesterol and PBI. However, the gland is hyperplastic and extremely avid for iodine so that when a dose of radioiodine is administered, a greater than normal percent is picked up by the cells (thyroid I–131) and converted to radiohormone (serum conversion ratio).

PATIENT 3 also represents an instance of dietary iodine deficiency but of greater severity or longer duration. So little iodine is available that, despite the efforts of the thyroid gland to compensate by hyperplasia and increased rate of hormonal synthesis, the amount of hormone produced is too low to maintain the patient in an euthyroid state, and hypothyroidism develops. As in the case of Patient 2 the gland enlarges and its increased avidity for iodine is mirrored by the elevated radioiodine uptake and conversion ratio. The symptoms of hypothyroidism are accompanied by a lowered BMR, an elevated cholesterol and, of course, a low level of circulating protein-bound iodine.

PATIENT 4 resembles Patient 2 in many ways. He, too, is euthyroid in the presence of an enlarged hyperplastic thyroid gland but the gland is unable to pick up iodine and synthesize hormone. Obviously, something is blocking the uptake of iodine by the gland leading to thyroid hormone deficiency and TSH increase. These are the findings of patients under the influence of thiocyanate whose iodine deficiency is mild and whose glands are able to compensate.

PATIENT 5 demonstrates a similar block of iodine uptake and conversion into hormone but in this instance hypothyroidism has developed despite the enlargement of the thyroid gland. The thyroid I–131 uptake and conversion ratio are low, as is the serum PBI; decompensation has developed. One finds such a set of studies in a patient with a complete or almost complete block of the trapping mechanism such as might occur after large amounts of thiocyanate over a long period of time.

TABLE 1.—THYROID FUNCTION STUDIES

Pt. No.	*Symptoms*	*Gland Size*	*BMR*	*Serum Chol.*	*Thyroid I–131*	*Serum Conv. Ratio*	*Serum PBI*	*Diagnosis*
1.	N	N	N	N	N	N	N	Euthyroid
2.	N	+	N	N	+	+	N	Iodine lack-euthyroid
3.	—	+	—	+	+	+	—	Iodine lack-hypothyroid
4.	N	+	N	N	—	—	N	Thiocyanate-euthyroid
5.	—	+	—	+	—	—	—	Thiocyanate-hypothyroid
6.	N	+	N	N	+,N	—	N	Thiouracil-euthyroid
7.	—	+	—	+	+,N,—	—	—	Thiouracil-hypothyroid
8.	—	—,N	—	+	—	—	—	Hypothyroid—Thyroid or Pituitary
9.	+	+	+	—	+	+	+	Hyperthyroid
10.	+	N	+	—	—	—	+	Thyrotoxicosis factitia
11.	+	N	+	—	—	+	+	Hyperthyroid-extrathyroidal (struma ovarii)
12.	N	—,Nod	N	N	+	+	N	Thyrotoxic remnant-euthyroid
13.	—	—,Nod	—	+	+	+	—	Thyrotoxic remnant-hypothyroid

— = decreased N = normal + = increased Nod = nodule

PATIENT 6 shows studies which are identical with Patient 4 (block of the trapping mechanism due to thiocyanate) excepting that the thyroid radioiodine uptake is normal or elevated. Here it is apparent that the patient is able to trap iodine but is unable to synthesize it into thyroid hormone normally as evidenced by the depressed conversion ratio. This is seen with thiouracil therapy or because of an inherent error in synthesis as in certain types of colloid goiter. Because of the lowered circulating hormone, the gland compensates by hyperplasia and under those circumstances is able to produce enough thyroid hormone so that the patient is euthyroid.

PATIENT 7 represents an exaggerated picture of faulty hormonal synthesis so that despite the ability to trap iodine and the hyperplasia of the gland the thyroid is unable

to produce enough hormone to maintain an euthyroid state. The thyroid gland is decompensated so that symptoms of hypothyroidism are present with a depressed BMR, an elevated serum cholesterol and a low protein-bound iodine level. These are the findings of patients made myxedematous with thiouracil and many goitrous cretins.

PATIENT 8. Certain patients with hypothyroidism are born without thyroid glands (nongoitrous cretins); others develop atrophy or destruction of the gland. Under these circumstances the gland is unable to trap and, therefore, to convert iodine into hormone as manifest by the depressed I–131 uptake and conversion ratio and low levels of PBI. Symptoms of hypothyroidism together with a low BMR and elevated cholesterol are to be expected. In this case the thyroid gland will not be enlarged indicating that hyperplasia is not possible. This, as mentioned above, is due to an inherent fault in the thyroid gland but it may also result from a defect of the anterior lobe of the pituitary gland so that TSH is not elaborated in sufficient quantities. The manner in which primary thyroid myxedema is differentiated from pituitary myxedema will be discussed below.

PATIENT 9 is thyrotoxic; symptoms of hyperthyroidism are present and the BMR is elevated and the cholesterol depressed. Whereas an elevated BMR together with suggestive symptoms may be found in anxiety and other extra-thyroidal hypermetabolic states, one does not expect the cholesterol to be depressed. Furthermore, the gland is enlarged in this individual indicating hyperplasia; increased amounts of radioiodine are trapped and converted and the level of circulating PBI is high. These are, of course, the findings typical of hyperthyroidism. When the glandular enlargement is of a diffuse type, the picture is that of Graves' disease; if a nodule is palpable one must then differentiate between diffuse toxic goiter with a nodule and toxic nodular goiter. The importance of the differentiation and the method by which this is accomplished are discussed below.

PATIENT 10 is extremely interesting and is the type which may present a real diagnostic dilemma. It is apparent that certain findings (symptoms, BMR, cholesterol and PBI) indicate hyperthyroidism but the radioiodine uptake and conversion ratio are depressed and the gland size is normal. The author has never seen a patient with frank hyperthyroidism without definite enlargement of the thyroid gland, and the normal gland size indicates absence of hyperplasia. It is apparent that the source of this patient's thyroid hormone excess is not the thyroid gland nor, in fact, from within the body, otherwise the conversion ratio would be elevated. These studies are typical of thyrotoxicosis factitia. The symptoms and metabolic changes are caused by the exogenously administered thyroid hormone and the serum PBI is also spuriously elevated on this account. The gland is normal in size since it does not enter into the hyperthyroid process and the radioiodine uptake by the thyroid gland and its conversion to radiohormone are depressed because the desiccated thyroid medication is depressing the thyrotrophic hormone production of the pituitary gland.

PATIENT 11 should now not be difficult to diagnose. The studies are identical with those of Patient 10 excepting for one finding, namely, the increased conversion ratio. This indicates that the thyroid hormone which is causing the toxicity *is* being produced within the body, but the normal gland size and depressed I–131 uptake tell us that the thyroid gland is not the source of the hormone. As a matter of fact, the thyroid gland is functioning at a lower than normal level. This means that the thyroid hormone is being produced in some area within the body other than the thyroid as, for example, in an ovarian teratoma. Teratomas often contain thyroid tissue and when this tissue becomes thyrotoxic (struma ovarii) iodine is synthesized into thyroid hormone in large amounts and the patient becomes thyrotoxic with an elevated conversion ratio. However, when a radioiodine tracer test is performed the Geiger counter is placed over the neck and so the hyperfunctioning ovarian thyroid tissue is missed completely.

PATIENTS 12 AND 13 illustrate the findings not uncommonly seen in individuals treated for thyrotoxicosis by means of surgery or radioiodine (Nodine *et al.*[4]). Under these circumstances the surgeon, when performing a subtotal thyroidectomy, removes hyperplastic thyroid tissue, but the thyroid tissue he leaves in the neck is also hyperplastic. This tissue traps iodine and synthesizes hormone at a rapid rate, but the small amount of thyroid gland *in situ* is able to produce only enough hormone to keep the patient euthyroid. Occasionally, as with Patient 13, when too much tissue has been removed, the patient may become hypothyroid despite the fact that the tissue which remains in the neck is hyperplastic. Under these circumstances large amounts of radioiodine are trapped and converted by the thyroid gland and this is indicated by the elevated I–131 tracer and

conversion ratio. The clinical status of the patient in these cases is measured more accurately by the BMR, cholesterol and serum protein-bound iodine.

Other interesting discrepancies in thyroid function studies have been reported. Patients with thyroiditis of the DeQuervain type will often show a markedly depressed I–131 uptake but with a high circulating PBI (Werner[8]). It has been suggested that the elevated PBI is due to sudden outpouring of iodine caused by destruction of the thyroid gland. A nonthyroxin-producing goiter with hypothyroidism has been described recently (Stanbury, Ohela and Pitt-Rivers[7]). The radioiodine tracer study, the conversion ratio and the PBI are all elevated; the protein-bound iodine in this case representing, however, an abnormal type of thyroid hormone which is metabolically inactive. It appears likely that other combinations will be added to this listing as time goes on. One set of findings, for example, which are seen occasionally include the signs and symptoms of thyrotoxicosis with a high PBI, a normal I–131 uptake study but a markedly elevated conversion ratio. These studies are typical in patients whose rate of hormone secretion is so great that there is never enough I–131 left in the thyroid gland to give a high 24-hour value. Patients with thyroid hormone-producing thyroid carcinoma and thyrotoxicosis may also demonstrate these findings.

One diagnostic procedure which has not received the application it deserves and which at times is extremely helpful in elucidating the role of the thyroid gland in the pathogenesis of heart failure is the circulation time. This test is of particular value in the elderly patient with cardiac decompensation, tachycardia, hypertension and an enlarged thyroid gland. In an individual with heart failure one expects the circulation time to be slowed whereas in thyrotoxicosis it is usually rapid. Consequently, if in such a patient the circulation time is normal or indeed rapid one must assume a high output type failure of which hyperthyroidism is the most likely etiologic factor.

When discussing Patient 8 with hypothyroidism, it was suggested that a differentiation between thyroid and pituitary myxedema could not be made by means of these studies. Whereas this is literally true, the 24-hour thyroid I–131 uptake is generally higher and the serum cholesterol lower in pituitary myxedema than in thyroid myxedema. A definitive differential diagnosis can be made only with the help of exogenously administered TSH (Despopoulous and Perloff[3]). A radioiodine uptake study or serum PBI is performed; TSH is then administered and the studies are repeated. In thyroid myxedema, since the thyroid gland itself is at fault and is unresponsive to pituitary stimulation, the tests before and after TSH will be similar. Contrariwise the thyroid gland has the capacity for stimulation but lies dormant because of lack of pituitary TSH in pituitary myxedema, so that when exogenous TSH is administered the post treatment studies are considerably higher than the control procedures. Of considerable interest is the fact that when a patient's thyroid is being blocked by iodine, TSH will cause a rise in PBI but no increase in I–131 uptake; but, when the gland is blocked by desiccated thyroid, TSH will cause an elevation of both the uptake and PBI. TSH may be employed advantageously in another type of diagnostic problem, namely, equivocal hypothyroidism where studies are borderline and where the physician is uncertain about the patient's clinical status (Schneeberg, Perloff and Levy[5]). A rise in PBI or I–131 uptake after TSH is extremely suggestive of normal thyroid function

whereas similar studies before and after TSH administration indicate hypothyroidism.

The diagnosis of toxic nodular goiter is usual when hyperthyroidism is present and a nodule is felt in the thyroid gland. This is a misnomer; the diagnosis of toxic nodular goiter should be reserved for those patients in whom thyrotoxicosis is being produced by the nodule and should not be employed in individuals who have a diffuse toxic goiter in whom coincidentally there happens to be a nodule. This differentiation is not merely academic because a subtotal thyroidectomy is required with diffuse toxic goiter whereas nodulectomy may be sufficient when the nodule alone is the culprit. For the purpose of this differentiation a scintigram is extremely helpful. Figure 2 demonstrates a "hot nodule," the removal of which resulted in clinical cure.

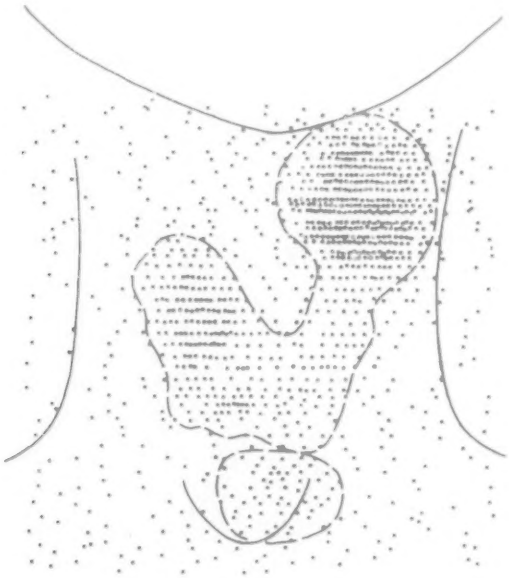

Fig. 2.—Scintigram of a "hot nodule."

Conclusions. This review of thyroid function studies was undertaken in an effort to clarify some of the misconceptions prevalent among practicing clinicians. Occasionally, a complete thyroid survey may be the only way in which to delineate an obscure diagnostic problem. The radioiodine thyroid uptake, the serum conversion ratio and the serum levels of protein-bound iodine are usually the most reliable tests of thyroid function. It must be admitted that the discerning clinician who does not allow himself to be stampeded into therapy can usually arrive at the correct diagnosis without the use of any of these complicated and expensive procedures. A therapeutic trial with thyroid alternating with a placebo will generally serve to distinguish patients with hypothyroidism from those with fatigue and inertia from other causes. By and large the diagnosis of hyperthyroidism is clearly manifest when the patient first confronts his physician. If the hyperthyroidism is so mild that the physician cannot determine whether or not the patient is truly thyrotoxic, it would be

well to wait until the metabolic disorder shows its hand more clearly, since under these circumstances the hyperthyroidism is of no immediate danger to the patient unless it is associated with cardiac insufficiency, tuberculosis or diabetes. Once therapy, as with thiouracil, is begun, the clinician is committed to a long course of treatment. It is, therefore, to be urged that a definitive diagnosis be established prior to the initiation of therapy, clinically if that is possible, or if this cannot be done, then with the aid of some of the thyroid function studies which have been described in this report.

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SUMMARIO IN INTERLINGUA

Studios de Function Thyroide

Iste revista de studios del functiones thyroide esseva interprendite con le objectivo de clarificar alicunes del conceptiones erronee que es prevalente inter clinicos practic. In certe casos il es possibile que un complete investigation thyroide es le sol methodo pro obtener un delineation de un obscur problema diagnostic. Determinationes del acceptation de iodo radioactive per le glandula thyroide e del proportion de conversion seral e del nivellos seral de iodo seral es usualmente le plus solide tests del function thyroide. Sed il debe esser admittite que le sage clinico, qui refusa facer se victima de precipitate decisiones therapeutic, trova normalmente possibile establir le correcte diagnose sin usar ullo de ille complicate e costose procedimentos. Un essayo therapeutic con extracto thyroide in alternation con un medication fictive servi generalmente a differentiar patientes con hypothyroidismo ab individuos con fatiga e inertia debite a altere causas. A generalmente parlar, le diagnose de hyperthyroidismo es clarmente manifeste quando le patiente se presenta al prime consultation. Si le hyperthyroidismo es si leve que le medico non pote determinar si on non le patiente és vermente thyrotoxic, il pare recommendabile attender usque le disordine metabolic se declara plus apertemente, proque sub tal conditiones le hyperthyroidismo non representa un periculo immediate pro le patiente, providite que illo non es associate con insufficientia cardiac, tuberculosis, o diabete. Post initiar le therapia, per exemplo con thiouracil, le clinico se trova confrontate con le necessitate de un longe curso therapeutic. Pro iste ration il es a recommendar urgentemente que un diagnose definite es establite ante le therapia es initiate. Establir ille diagnose definite debe facer se clinicamente si possibile o, si tal medios non suffice, per alicunes del studios de function thyroide que es describite in le presente reporto.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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GERIATRIC OTOLARYNGOLOGY

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ONE of the striking consequences of the advances made by contemporary medicine is reflected in the longer life span of millions of Americans. Persons 65 years of age and older increased from 8 million in 1935 to 12 million in 1950. The geriatric population of the United States is expected to be 15 million by 1960 and 20 million by 1975. The projected increase is 150% as compared with an expected increase of 45% in the general population by 1975. Actually, the upper age group now accounts for approximately 10% of the general population (Schweigert[14]).

According to Monroe[8], if geriatrics is to become a distinct discipline among the medical arts and sciences, it must develop and constantly accumulate a body of facts and methods comparable to those which make up pediatrics. Although geriatrics as a special field in medicine has attracted mounting interest in various quarters, gaps are still extant. Since relatively little has been written about geriatric otolaryngology, the purpose of this review is to summarize some of the published communications that have appeared recently.

A study of the incidence of ear, nose and throat diseases in older persons by Hollender and Lytton[5] reveals that ear problems exceed those involving other structures, with the dominant complaint dealing with impaired hearing. Along with deafness as one of the entities intensified by the lengthened span of life are the symptoms of vertigo and tinnitus. Evidence of nasal and sinus operations was seen in approximately 12% of patients encountered in office practice. The operation that had been most frequently performed was septal resection. Although most nasal complaints dealt with such self-limited conditions as the common cold, chronic rhinosinusitis was de-

tected in 20% of office patients. Common symptoms included nasal stuffiness, postnasal discharge, headache, hawking, and coughing. Nasal allergy was only occasionally diagnosed clinically. In 10 to 15% of the patients atrophic changes in the nasal mucous membranes were observed. Since many patients had submitted to intranasal surgery during youth or middle age, it was difficult to determine whether the atrophic changes were due to surgical intervention or to natural aging changes. Tonsillitis occurred infrequently, and few patients complained of sore throat. Hoarseness was not an uncommon finding, being associated with the common cold, fatigue, overexertion, and general debility. In the age group between 75 and 90, a weak, unnatural voice was the rule, the change becoming more pronounced as age advanced. Chronic hoarseness occurred in approximately 1 out of 12 patients. Benign tumors and granulomas of the larynx were found in 8 of 100 patients, while 7 evinced laryngeal carcinoma, one patient revealed syphilis, and two had tuberculosis of the larynx. Epistaxis provided one of the more frequently encountered emergencies, presumably because of coexistent hypertension. External otitis occurred infrequently. It was concluded that older persons are, with few exceptions, subject to the same types of inflammatory diseases of the upper respiratory tract as are younger persons. Poos[12] states that tinnitus is common in older persons afflicted with cardiovascular disease, cerebral arteriosclerosis, anemia, and allergic and toxic states, and may follow trauma to the head, which is a frequent complaint of emotional and psychotic patients. He often found glossodynia, paresthesias, burning tongue, riboflavin deficiency glossitis, geographic tongue, and atrophic glossitis present in older persons. It was often difficult to determine how many symptoms were due specifically to the aging process and how many attributable to other factors.

Alexander[1] maintains it is fortunate that the accentuation of the hearing problem has coincided with the fresh outlook on deafness which currently characterizes sound otolaryngological practice. The defeatist attitude with which the hearing handicap was formerly associated has almost completely disappeared, a major reason being that otologists have become increasingly aware of the seriousness of hearing loss to the individual patient himself. According to Alexander, one of the objectives of the relatively new specialty of geriatrics should be the relief of the deafened older age-group patient. At present, it is admitted that only in occasional instances is any form of treatment likely to produce a cure or even significant improvement if hearing impairment is total or nearly so. Although the fenestration operation represents an important surgical advance in the treatment of otosclerosis, its usefulness is limited, for the procedure has nothing to offer the vastly larger group of patients with nerve deafness. Aural rehabilitation, on the other hand, offers a great deal to the latter group. Relief of deafness in aging persons should be a co-operative venture, with otologists playing a prominent, helpful role. As for treatment, promises of cure and relief should be uttered by physicians in measured, guarded terms. Older patients should be advised that much can be done to make life more tolerable, but they should never be informed that deafness, regardless of the type, is curable. Deafness is inherently a psychic as well as a physical affliction. To permit patients to suffer serious disappointment, because therapy is bound to be

associated with failure, would merely enhance that aspect of the defect.

While there are many other contributing factors, including otitis media, otosclerosis, acoustic trauma, neoplasms, medication, vascular disease and cerebral injury, presbycusis is the most frequent cause of deafness in older persons. In presbycusis there is a loss of hearing for high-pitched tones due to advancing age, said to occur at the rate of loss of one decibel for each year of life. It may occur in middle age in predisposed persons and is due to arteriosclerotic and degenerative changes. Histologically, presbycusis is associated with atrophy of the ganglion cells, changes in the hair cells in the basal coils of the cochlea, and changes in the blood vessels of the acoustic nerve.

The onset of presbycusis is insidious and its rate of progress slow. The complaint of deafness is frequently greater than carefully conducted hearing tests would normally suggest. On the other hand, lack of attention on the part of older persons seems to increase the apparent hearing defect and, consequently, difficulty due to confusion of sounds ensues. In general, in older persons the hearing loss averages 40 decibels. Associated nerve loss is the cause of poor discrimination with respect to speech.

In a study aimed at a clinical evaluation of presbycusis on the basis of different tests of auditory function carried out in 185 older persons, Pestalozza and Shore[10] found that in old persons discrimination for speech is very poor, even in the presence of a mild hearing loss. In old persons a clear relation exists between hearing loss and discrimination loss; discrimination becomes poorer as hearing loss becomes greater. No significant relation was found between slope of the audiogram and discrimination loss. In a smaller group of 24 old persons in whom a recruitment test was performed, 50% of the subjects showed no recruitment, 30% partial recruitment, and 20% almost complete recruitment. The absence of recruitment in most patients with presbycusis is in keeping with histological findings in spiral ganglion cells and nerve fibers as the most common lesions responsible for hearing loss in recruitment. Since treatment will neither prevent nor reverse the loss of hearing in older persons, Simonton[15] asserts that careful enunciation by the speaker, avoidance of confusing noise, speech reading (commonly called "lip reading") and the use of a hearing aid will help the person suffering from presbycusis.

Arteriosclerotic deafness is, in the main, a disease of older persons, being present unilaterally or being more pronounced unilaterally in most instances. Tinnitus is likely to occur in the more severely affected ear, and this often provides a clue to the diagnosis. Hearing loss occurs for all frequencies because sclerosis of the internal auditory artery, which supplies the labyrinth exclusively, affects the entire cochlea and diminishes its total performance. Although secondary nerve degeneration takes place after vascular degeneration, it is important to interpret this finding in the light of slower cerebration associated with the advancing age status.

The incidence, causes and effects of vertigo on an elderly population were studied by Droller and Pemberton[3]. Their observations were based on medical examinations of 476 elderly persons living in their own homes, either alone or with their spouses. In the majority of people, vertigo appeared to be closely associated with arteriosclerosis of the labyrinth. In a smaller number of subjects a drop in blood pressure on changing from the

supine to the upright position brought on an attack. Typical Ménière's syndrome was rare. In a few subjects several vertigo-producing factors operated simultaneously.

Kelemen[7] states that the tonsil generally does not attain total involution during a lifetime. In the curve of tonsillar involution, a plateau is found corresponding to the period between 45 and 65 years of age. Involution in the palatine tonsils is an atrophic process, cells decreasing in number and tissues in size without degeneration and without reverting to a functionally less active form before final disappearance. Scarcity of thromboses in veins and of perivascular infiltratons in the retrotonsillar space accounts, together with the diminishing mass of tonsillar tissue, for the infrequency of local reactions around the receding tonsil. At the same time, with parenchymal activity qualitatively unchanged, focal reactions appear in distant organs of the body as they do at any age. Operation on tonsils in persons of advanced age is a relatively unexacting procedure, to patient and surgeon. No greater operative risk is involved than in younger persons.

The mouth is subject to changes with age, as are other parts of the body. Robinson[13] declares that the number of missing teeth per person increased with each decade of life, until, at age 70, 80% of women and 70% of men have lost all their teeth. At younger ages the teeth are lost chiefly because of dental decay, but in older persons periodontal disease provides the most important cause for extraction. Aging appears to be more important etiologically in attrition, abrasion and traumatism than in caries, erosion and periodontosis. Disease processes may accelerate age changes in the mouth, and, conversely, age changes may afford greater opportunity for invasion by microörganisms.

Mild degrees of nutritional deficiency frequently occur in elderly people who live alone, but gross deficiencies like scurvy and pellagra are rare. Hughes and MacLennan[6] describe a case of scurvy in an elderly man with mental deterioration, living alone after the death of his wife, and whose home showed no evidence of recent cooking. The scurvy and his general condition improved after treatment with vitamin C and later with iron and vitamin B complex, but his mental condition remained unaltered. In this case, funds were available to provide an adequate diet had he been mentally competent to spend money for this purpose. In other instances cited, scurvy in elderly persons resulted from diets limited to tea and bread, occasional meat, and without vegetables and potatoes.

Simple chronic bronchial irritation, state Phillips and his associates[11], appears to be the most common cause of chronic cough. Chronic bronchitis frequently causes pulmonary emphysema. Among 18 males aged 50 to 69 years, who coughed for ten or more years, the inhalation of cigarette smoke was found to be the common agent in the production of chronic bronchitis. No other cause for chronic cough was demonstrated. All 18 patients raised excessive sputum and showed evidence of pulmonary emphysema. A study of 20 cases with necropsy evidence of pulmonary emphysema and without tuberculosis, tumor or asthma, showed chronic bronchitis in all subjects. Bronchiectasis was found in two patients.

Otolaryngologists are often concerned with various skin diseases pertaining to the head and neck. Aging of the skin, which is the most evident of all the aging processes that occur in the body, may be brought on pre-

maturely by environmental trauma. Protection of the skin from chronic low-grade overexposure to sunlight or to ultraviolet light is of great importance. Freeman[4] declares that the major distinctive problems of aging skin are disturbances in the growth pattern, which result in retrogressive functional and anatomic changes typical of atrophic aging tissue and in a unique group of proliferative disorders. The common dermatoses also frequently affect the skin of the elderly. Dryness of the skin is common past the age of 35 years. The associated pruritus, when persistent, may indicate internal disease. Proliferative changes require close medical attention.

One out of every three elderly patients seen because of skin changes will have either a senile keratosis or a true epithelioma. Senile keratoses, which are considered precancerous, occur as red, scaly lesions of the exposed or aged skin. Epitheliomas appear as solid growths, with or without ulceration, and usually occur on exposed sites where aging is most advanced. Biopsy study is necessary to confirm the diagnosis and to determine the exact nature of the growth. The more common basal-cell epithelioma is localized and does not metastasize; on the other hand, the squamous-cell epithelioma is a serious malignant growth of the skin and may metastasize. Both types of epithelioma require complete removal either by surgery, irradiation, or electrocoagulation. Seborrheic keratosis rarely requires treatment other than for cosmetic reasons.

Percival[9] maintains that pyogenic infection rarely occurs in senile skin. Herpes zoster may lead to persistent debility. Urticaria, although rare, tends to be intractable, while senile pruritis occurs in the lean and emaciated. Diffuse neurodermatitis is seldom seen in the elderly. After the age of 50, dermatitis herpetiformis carries a 40 to 50% mortality rate. Primary atrophy of the skin usually occurs in old age. The lesions of hypertrophy of the stratum corneum form small warty keratomas, and these should be destroyed since they are considered precursors of squamous-cell carcinoma.

Age by itself produces no significant change in the blood forming organs. Increase in the sedimentation rate, thought to be due to blood protein alterations, is the only consistent finding associated with the aging process. Cooper[2] states that the bone marrow in the aged shows no qualitative difference from that of younger persons. The mechanisms of anemia in the aged are the same as in other age groups. Nutritional deficiency is a frequent cause. Achlorhydria, which occurs in many older persons, may cause diarrhea, distention and anorexia to initiate a nutritional deficiency syndrome. Pernicious anemia has an incidence as high as 72% in persons beyond 50 years of age. So-called "shot-gun" medications comprising folic acid, gastric substance, and vitamin B_{12}, in combination with iron and vitamins, may contain sufficient erythrocyte maturation factor to correct the anemia partially and to alter completely the typical morphology of blood and marrow, but not enough to control the neural and central nervous system symptoms of the disease. The resulting atypical clinical and hematologic findings and bizarre neurologic manifestations can only be proved to be those of pernicious anemia by the response to parenteral administration of vitamin B_{12} and liver extract. It is concluded that there is no justification for the designation "anemia of old age."

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SUMMARIO IN INTERLINGUA

(See page 389 for original article)

Observationes in Re Certe Possibile Precursores de Hypertension Essential e Morbo de Arteria Coronari: V. Hypercholesteremia in Juvene Adultos Normal

Le constatationes pare indicar: (1) Que le emergentia del tracto hypercholesteremic in juvene individuos es associabile con un tendentia familial a morbo cardiovascular, specialmente morbo coronari, e a diabete.

(2) Que hypercholesteremia se manifesta quando le crescentia physic e maturation sexual es complete e quando alterate factores ambiental es presente que produce augmentos del nivello de cholesterol in certe individuos e non in alteres.

(3) Que le individuos qui es susceptibile al influentia de tal factores ambiental heredita probabilemente un defecto metabolic, possibilemente del cortice adrenal, que promove hypercholesteremia e atherogenese e in le curso del tempore pote causar le disveloppamento de morbo del arteria coronari, hypertension, e diabete, individualmente o in varie combinationes.

(4) Que juvene adultos hypercholesteremic pote esser identificate per periodic determinationes del nivello seral de cholesterol.

(5) Que mesuras destinate a mantener normal nivellos de cholesterol in tal individuos, ben que possibilemente efficace in alterar le subsequente disveloppamentos pathologic, es probabilemente incapace a alterar le defecto metabolic fundamental.

DERMATOLOGY AND SYPHILOLOGY

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A RE-EVALUATION OF THE ROSACEA COMPLEX

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ROSACEA, often called acne rosacea, is a disease which has been known for many years. Bulbous noses (rhinophyma) have been mentioned in classical English literature and depicted in works of art. In spite of the antiquity of this process and its prevalence (½ to 1% fresh cases of skin disease[93a]) controversial literature has been developed about it. Part of the cause for the differences of opinion concerning this disease in the medical literature is the fact that at various times some authorities have championed the idea that rosacea is indeed a simple, superficial, inconsequential process caused by an equally unimportant, easily removed factor, for example, *Demodex folliculorum*[7a,7b], or the effect of climatic agents on the facial skin[93a]. The reviewer has had an intense interest in rosacea for more than 25 years. He is convinced from a study of all the available data that rosacea is not only a disease of frequent occurrence but is also an important internal medical disorder with expressions in many systems: gastrointestinal, nervous system, eyes and vascular system. In 1932, Stokes and Beerman[96] made an appraisal of rosacea with special reference to the constitutional background and the rationale of treatment. In this study there was a striking variety of factors (especially nervous, gastrointestinal and seborrheic) which were involved in the individual patient, and we reaffirmed the conclusion already expressed in the literature that the rational treatment of rosacea must concern itself chiefly with the constitutional indications. (*Cf.* Sellei[88]). Ayres and Anderson[7b], however, stated that it was "not necessary to search so widely for the cause of the condition in most cases." They added that one

has only to examine a small droplet of pus obtained from a superficial pustule to find numerous *Demodex folliculorum* organisms, and that local antiparasitic treatment has given clinical results far surpassing anything in their experience with the disease. We[10] in 1934 studied a new series of rosacea patients from the standpoint of constitutional and local parasitic factors and found that the constitutional factors were present in about the same frequency as in the earlier series and that *Demodex folliculorum* was not present in more patients with rosacea than in the controls, that is, in greater numbers than in 29 non-rosacea persons, including fourteen normal individuals. Now, after about 20 years, evaluation of the newer contributions dealing with rosacea is in order. In this compilation it is intended to define the clinical complex of rosacea as well as to discuss its pathogenesis and therapy.

CLINICAL COMPLEX OF ROSACEA. Rosacea clinically is a facial disorder which early in its evolution is manifested by transient episodes of erythema and vasodilatation. Some time after onset of the process (months to years) papules and pustules appear and the follicular orifices become conspicuous. Oily seborrhea of the face is a frequent accompaniment. The erythema, transient at first, may exacerbate from heat, cold and other factors at frequent intervals, only to become permanent later on. The dilated vessels also remain as telangiectasia. Subjective symptoms are minimal. Rhinophyma develops in some long-standing cases. This is characterized by an increase in size of the nose, often in regular fashion but occasionally in the form of irregular, lobulated masses, dusky red or purple in color ("rum blossom"). The sebaceous orifices are widely dilated. Rhinophyma may be the sole evidence of the existence of the process.

In addition to the cutaneous manifestations, there are variable percentages of associated complaints in patients with this disease. In our first series of cases[96] we found that the following factors ranked as major influences: the seborrheic habitus (80%); nervous factors (76%); and gastrointestinal disturbances (66%). In the 1935 series[10] we found the seborrheic habitus present in 83%; the nervous factors in 65.2%; and the gastrointestinal disturbances in 48%. Focal infections were noted in 51.9% and 22% in the two series, respectively. Ocular complaints, while noted, were not an outstanding accompaniment of rosacea in our groups. Rosacea was found to appear in the majority of cases early in middle life (68 of 83 patients averaged 32.1 years), but it may appear in childhood (10 years) or old age (68 years). The onset is slow in two-thirds of the cases; in others it may be rapid but not explosive. Certain investigators, too, have observed these and additional etiologic factors which have been thought to play a role in the causal background of rosacea. The following is a partial listing of the reported data:

Focal infection[31,106].
Emotional and nervous states[10,23,50,79,96].
Gastrointestinal disturbances[9,57,102].
Lowered or otherwise altered gastric acidity[30,70,75].
Gastroscopic findings[22,101].
Liver dysfunction[5,33].
Endocrine changes[13,59,75,102].
External mechanical factors, for example, exposure to sun, cold and wind[49,57,75,81,93a].
Disorders of the fifth nerve[75,104a,104b].
Vasomotor instability[14b,14c,27,32,33,98].
Angiopathy[36].
Virus[60].
Demodex folliculorum[7b,15,17].
Vitamin B_2 (riboflavin) deficiency[12,26a,26b,26c,45].
Allergy. Hormone allergy[40a,109].
Bacterial allergy[4a].
Intestinal carbohydrate intolerance[96].

In spite of the wealth of data indicating the multiple causal background or rosacea, there have been attempts to establish this process as a really simple situation. As previously mentioned, Ayres and Anderson, as well as others, have suggested that *Demodex folliculorum* is *the* cause of roacea. More recently, Søbye[93a] on the basis of a really extensive experience with this disease (128 patients; 75 biopsies; detailed past histories and numerous examinations) concluded 1) that there is no relationship between diseases of the digestive system and rosacea; 2) that there is no relationship between the ordinary form of rosacea and overindulgence in tea, coffee, tobacco, alcoholic drinks, substantial meals, and spiced food; 3) that rosacea is independent of lesions in ovaries and uterus, and of menorrhagia, whereas the menopause probably plays a certain part in some of the cases; 4) that rosacea comparatively rarely is associated with seborrhea, but that in the 20% where it is observed, he cannot exclude the possibility that seborrhea may influence the picture; 5) that there is no relationship between rosacea and focal infection; 6) that rosacea is not due to bacterial infection; 7) that rosacea (on the facial skin) is unlikely to be an avitaminosis; 8) that psychic factors and traumas generally have no influence on the development of rosacea, but many rosacea patients suffer from inferiority complexes and shun the society of other people owing to their disfiguring skin lesions. He showed that rosacea probably owes its occurrence to the fact that a prolonged influence of climatic agents on the facial skin will bring about a more or less pronounced injury to the vessels, causing oozing of fluid which cannot be removed in a normal way but remains as edema in the affected areas, where the facial muscles move very little or not at all. Treatment of rosacea patients by massage and muscular exercise has a favorable effect. This may be explained by the fact that the massage manipulations effect removal of the edema from the tissue after which the facial muscles, put more or less out of action, can begin to act normally and thus contribute to keep the tissue free of edema.

Perhaps Ayres'[6] recent analysis of rosacea comes nearest to the proper interpretation of this disease. He now believes in a compromise situation whereby there are both "external" and "internal" types of rosacea. The external type is caused by *Demodex folliculorum* and is easily managed by local measures. The internal type is usually associated with a variety of factors such as were previously mentioned. However, as Søbye's[93a] experience would suggest, there are probably other external causes besides *Demodex folliculorum*.

The fundamental abnormality in cutaneous rosacea is vasodilatation in the central area of the face, presenting as an increase in the depth of color. Such a color change is due to dilatation of the most superficial vessels, capillaries, venules (Lewis 1927)[58] with or without dilatation of the arterioles. Not certain about the vessels in rosacea (arterioles), Borrie[14b] studied the state of the arterioles in 26 patients with rosacea and 26 normal controls. He measured face-skin temperature, at rest, after cooling the face, and after heating the body and limbs. No marked or constant difference in skin temperature was found between the two groups. These temperature studies suggest that the arterioles play no part in the pathogenesis of cutaneous rosacea. Borrie[14c] also studied the effect on the facial blood vessels of various substances (hormones), adrenaline, noradrenaline, histamine and acetycho-

line introduced locally, and carbaminoyl choline injected systemically, in 17 patients with rosacea and controls. No significant difference was found in results produced in both groups.

It is suggested by Wise[107] from his study of the problem that rosacea is due to some factor, at present unknown, that produced prolonged vasodilatation of the superficial vessels in the so-called blush area. The papules and sebaceous gland hypertrophy probably are secondary to the congestion in this region incident to the prolonged vasodilatation. The pustules of the face and the infectious ocular changes undoubtedly are entirely secondary and play no part in the fundamental cause of rosacea. Telangiectasia occurs when the vessels' contractile power is finally completely exhausted. This does not explain the new vessel formation in the cornea, but the latter appears to be a reasonable response by an avascular tissue to some unknown stimulus that causes an increase in the vascular bed of a vascular tissue through vasodilatation.

Miller[74] discusses some of the possible nervous pathways affecting vasodilatation of the face. It is known that nerve impulses pass more easily over a given pathway following each successive passage. In this way some individuals having an inherently labile tonus of the facial blood vessels would, through repeated blushing, flushing after meals, and the like, increase the ease with which impulses could pass over this course. Miller also mentions the interesting possibility of overflow of afferent impulses to the brain along such a path of least resistance. Possibly the fifth nerve has a lower threshold for eliciting a response than have other nerves, and for this reason is more often stimulated to activity.

Numerous other authors[27,57,71,75] have stressed this vasomotor factor, Eastwood[28] wondering ". . . whether rosacea is an end result of an abnormal response to a natural stimulus," and Verhoeff[104a,104b] suggesting that ". . . possibly noxious agents act on the Gasserian ganglion, which sets up stimuli which pass back down the nerve and cause the lesion at its termination."

At any rate, vasodilatation of the facial vessels, whether brought about by impulses passing via the fifth nerve, the cervical sympathetic, or some vasoconstrictor or vasodilator "center" in the brain stem, is a very complex and little understood mechanism at this time. Wise[107] suggested that it would be most interesting to see the effect on rosacea of interrupting the vasodilator pathway to the blush area of the face, if this could be done.

According to Ramel[80] clinical observation of the postprandial erythema in cases of rosacea suggests that certain substances escape the neutralizing effect of the digestive juices and are absorbed into the blood in a form which gives them a vasodilator activity; histamine will have to be taken into consideration in this respect, since subcutaneous injection of 1.0 mg. of histamine provokes temporary congestion of the face.

Søbye[93a] has summarized additional explanations for the vascular reaction in rosacea. Unna[100] supposed rosacea to be due to an arterial paralysis in association with seborrhea and infection. Haxthausen[38a] pointed out that hyperemia and telangiectasis together with degeneration of the elastic tissue of the skin constitute three of the most characteristic effects of light. He stated that, "Thus light tends to cause a steady and chronic aggravation of the lesion. In addition, however, it gives rise to acute exacerbations, and it should no doubt also in a number of cases be regarded as the agent which first pro-

voked the disease." In a subsequent paper Haxthausen[38b] stated that many cases of rosacea simply represent a particularly pronounced degree of the chronic changes due to light and cold in the vessels of the facial skin. Finally, Haxthausen[38c] in yet another paper showed by means of skin temperature measurements and histamine tests that isolated, chronic exposure of the skin to cold brought about dilatation of the capillaries, manifesting itself by a flush with or without attending cyanosis, and contraction of the small arteries, manifesting itself by a slight fall in the skin temperature. Isolated, chronic exposure to light also caused a permanent dilatation of the visible vessels manifesting itself by a flush without cyanosis but with a tendency to particularly easy dilatation of the arteries. Chronic exposure to heat had the same effect. Exposure of the skin to both cold and sunlight, as is the case in the face, brought about a permanent dilatation of the capillaries and the small veins, whereas the small arteries were contracted by cold and dilated by sunlight. While the cold had an influence particularly on the nutrition of the skin and skin lesions of hematogenic origin, the light seemed rather to predispose to exudative skin lesions. In the face, where both cold and light acted jointly, it was difficult to decide which agent had the greater share in the vascular changes found.

Lewis[58] claimed to have ascertained that the vessels of the subpapillary layer lost their contractile power and he found that by local application of epinephrine the small veins would not contract and the vessels which did contract were dilated far more easily than normal by cupping.

MacLeod[67] and Whitwell and Shone[106] found frequent coincidence of rosacea and perniosis, and they declared that both conditions are characterized by the presence of infiltrations, papules, and telangiectasia. The superficial vessels were seen to be dilated by exposure to cold, which they regarded as the essential agent.

While Klaber and Wittkower[50] also regarded rosacea as a primary vascular lesion, where the superficial vessels in the predisposed individuals lose their contractile power, they were, however, of the opinion that lack of mental balance brought about by personal or social troubles plays the main part as an etiological agent.

In Stein's[94] opinion the hyperemia of rosacea should be due to angioneurosis. The vascular dilatation should arise by the trigeminal center being exposed to the action of poisons developed in consequence of digestive diseases, menopause, or ovarian lesions, and the like. At first only the superficial vessels should be dilated but later also the more deep-seated, and the color thereby change from bright red to bluish red. Not till after such a vascular dilatation, in predisposed individuals, do we, in Stein's opinion, find development of seborrhea, telangiectasia, papules, pustules, and finally fibrosis.

Anderson[2] held that the disease should be due primarily to a neurovascular instability and that the eruptions and exacerbations should have different extrinsic causes.

SEX. Most students of rosacea have noted the preponderance of females in their series. For example, Stokes and Beerman[96] found that women outnumbered men three to one. This was in agreement with the literature up to 1932. Since then Ramel[80], as well as others, noted the greater number of women. Wise[107] had 39 women and 21 men in his group. Cawley and Curtis[19] studied 212 females and 138 males. Søbye[93a] had 99 women and 29 men. Borrie[14a] found that ocular lesions were

more common in men. Stokes and Beerman[96] felt that the greater incidence in women was not due to an increased disposition of women to seek cosmetic advice, though this was suggested by Low[64]. They also noted that Vanzant[1] on the basis of 3000 normal persons, reported that women have a lower gastric acidity than men. Additional reasons given by them for considering women especially susceptible in the light of the foregoing analysis of the factors in the rosacea complex include 1) their relatively frequent exposure, so to speak, to carbohydrate and caffeine dependent on their responsibility for the bridge and tea activities of social life; 2) the irregular and often inadequate meals which result from their family responsibilities, which, of course, may well lead to the development of disturbances of gastric function; 3) the detail and the petty wear and tear, long dragged out, of the years of upbringing and disciplining of children, and 4) the marital problems of "mid-channel," both of which bring women toward the forties with a tendency toward vascular reactivity and irritable sympathetic mechanism, which probably underlie their predisposition in these years to rosacea and neurodermatitis. Menstruation and the menopause thus logically fall into the subordinate relation that the various authors have recognized.

SKIN COLOR. Reyn[81] believed that the importance of light as an etiological agent should be due to rosacea patients being poor pigment producers. He found that out of 60 rosacea patients, 47 were light-blond, 17 dark-blond, while only 2 were dark. Reyn confirmed that rosacea affects women three times as often as men. The former being poorer pigment producers than the latter, he took this as evidence in favor of his theory. The difference between the numbers of fair and dark was less pronounced among Søbye's[93a] patients (28% light-blond, 55% dark-blond, and 17% dark) although the blond were also here in the majority.

HEREDITARY FACTOR. There has been little further elaboration on the hereditary factor in rosacea since Stokes' and Beerman's[96] presentation. At that time it was found that only 4 of 38 patients of whom inquiries were made had familial trends. Fourteen, however, came of seborrheic stocks, five had pronounced nervous backgrounds, eight had a distinct familial predisposition to pyogenic infection, but none had gastrointestinal predisposition. While these data tended to discredit the conception of hereditary predisposition, it was felt that further inquiry might reveal more evidence in support of such a background. This is suggested by the large hereditary element in acne[1,91]. Seltzer[89] noted an hereditary factor in his patient with rhinophyma with an associated acromegalic condition.

SEBORRHEIC HABITUS. As stated in our 1932 report[96], we subscribe to the belief that the seborrheic habitus is a constitutional state, to some extent hereditary, in which abnormal activity of the sebaceous glands bears a relationship to the carbohydrate metabolism of the skin, and perhaps to that of the body as a whole. From the manner in which seborrheic processes respond to restriction of carbohydrate intake it is reasonable to suspect that the essence of the cutaneous abnormality in such persons may be a tendency to overstore the skin with carbohydrate, or, when it is stored, to metabolize it abnormally. A deeper defect may, of course, be suspected either in the mechanism of the liver, pancreas, muscles, and nervous system for the utilization of carbohydrate or in the flooding of a vasodilated area, as in rosacea, with an overload of carbohy-

drate from the circulation. It will be recalled that without a necessarily lasting rise in blood sugar, the skin was shown by Folin, Trimble and Newman to take up rapidly sugar introduced directly into the circulation. The patient with rosacea may thus react to carbohydrate because he is above all a seborrheic person with a localizing vascular disturbance.

The seborrheic habitus includes various forms of dermatitis involving the scalp and rosaceous areas of the face, and acne as such. One or the other condition was present in 80.2% of our patients with rosacea. Distinct seborrheic processes other than acne appeared in 48.1% and acne as such, or as scars, in 58%. Several patients had acne due to bromide from medicine prescribed for the neurogenous element. Rhinophymatous changes appeared in only 2 cases. In our second study we observed the seborrheic factor in 83% of 23 patients.

Since these publications, the seborrheic aspect of rosacea has been variously regarded. While many[4a,19,25,33,36,47,50,80] admit the coexistence of seborrhea in a varying percentage of patients with rosacea, Søbye[93a] felt that this process is associated with seborrhea comparatively rarely, although in 20% of cases where this lesion is observed he could not exclude the possibility that seborrhea may influence the picture. Klaber and Wittkower[50] note that, while some associate rosacea with seborrhea, rosacea is primarily a circulatory disorder and it seems unlikely that seborrhea could be more than a collateral or complicating factor. In their series, high degrees of seborrhea were only present in a minority of cases. Aron-Brunetiére[3] found rosacea to develop at an earlier age in cases of seborrhea. Cawley and Curtis[19] believe that there may be an underlying relationship between rosacea and the seborrheic state (oily seborrhea and seborrheic dermatitis). Ramel[80] has distinguished four types of rosacea, one of which is the erythematous, congestive type complicated by seborrheic eczema.

FOCAL INFECTION. It is most difficult to prove outright the causative influence of a focus of infection in a skin disease[29,43,40,52]. Although Stokes and Beerman[96] found definite foci of infection in 51.9% of their patients, the relationship of these foci was close in but few instances. The infected foci in this group were in the teeth, the sinuses, gastrointestinal tract and gallbladder. Feit, Laszlo and Vero[31] regarded rosacea as a "bacterid" from focal infection. They found in their series of 50 cases, peri-apical abscesses in 29, infection of the accessory sinuses in 13, and chronic tonsillitis in 12. Removal of the foci of infection was accompanied by complete clearing of the rosacea in 14 patients; 13 were greatly improved; 12 were improved; 1 was not improved; and 10 were not followed up. Klaber and Wittkower[50] did not see much evidence of focal infection in their patients but felt that this factor deserved more attention. Hellier[39] recommended a careful examination of the mouth, nose and throat for the presence of sepsis. He made it a point of transilluminating the sinuses of all cases which he sees suffering from rosacea and "any suspicious case is referred to the nose surgeon for *x*-ray, and, if necessary, for an exploratory antrotomy." Some of the patients in Wise's[107] group undoubtedly had focal infections. Certain of them had all foci removed as far as was possible without experiencing a notable change in the rosacea. Although there was transient improvement and flares in some cases at the time of removal of teeth, in over-all evaluation, the possibility that focal in-

fection could be important in the causation of rosacea was thought to be remote. Søbye (1950)[93a] categorically stated that there is no relationship between rosacea and focal infection.

DIET. The common idea is that rosacea is provoked by the ingestion of hot, spicy, and alcoholic foods and beverages. Søbye[93] as well as Cawley and Curtis[19] and Klaber and Wittkower[50] found no relationship of rosacea to hot, spicy foods or alcoholic drinks. Alcohol undoubtedly plays a minor role in this disease, partly by the atrophic gastritis produced by chronic alcoholism. Because alcohol ingestion may cause neglect of eating, it may, in addition, contribute to the vitamin B deficiency in rosacea, to be discussed later. Stokes and Beerman[96] were surprised to find that their rosacea patients, even with the seborrheic habitus, on the whole had their disease in spite of a lowered carbohydrate intake. This was explained on the basis of intestinal intolerance of carbohydrate, and emphasized by individual striking examples of relapse following free ingestion of carbohydrates.

Perhaps the most outstanding contribution to the dietary aspects of rosacea pathogenesis is the demonstration that this disease represents riboflavin or vitamin B_2 deficiency. Riboflavin combines with phosphoric acid to form an ester that unites with various body proteins to form Warburg's yellow respiratory enzyme. This enzyme is an important factor in tissue respiration and is especially important in the case of an avascular tissue such as the cornea. Johnson and Eckardt[45] have utilized 1 to 2 mg. of riboflavin administered intravenously for 6 to 8 days followed by oral doses of 5 to 20 mg. daily for successful treatment of cases of rosacea keratitis. Wise[107] who studied this problem concluded that rosacea is not a vitamin deficiency. This view was concurred in by Søbye[93a] for facial rosacea.

ENDOCRINE FACTOR. Although many observers have relegated menstrual disorders to a minor place as a causative factor in the rosacea complex, Cawley and Curtis[19] reported that 27 of the adult female patients had noted an apparent relationship between worsening of the rosacea and occurrence of the menstrual period. In 9 cases there was cessation of the rosacea with the onset of the menopause. They concluded that it seemed probable that an endocrine imbalance may play some role in the causal background of rosacea. Klaber and Wittkower[50] were not impressed with the endocrine factor. Likewise, Søbye[93a] as well as Wise[107] could not relate rosacea to endocrine (menstrual and pregnancy) factors. Søbye[93a] did indicate that the menopause probably plays a certain part in some of the cases. The previously cited work on sex hormones should be recalled here. The association of rhinophyma with acromegaly[89] in one case is not evidence of a strong endocrine basis of rosacea. The recent use of the adrenocorticotropic hormones in treatment of rosacea does indicate a possible relationship of this process to this group of hormones[46,87,97].

OCULAR COMPONENT OF ROSACEA. The ophthalmological manifestations have had recent collation by Wise[107]; by Cawley and Curtis[19]; by Goldsmith[35]; by Borrie (1953)[14a] and by others. The association of rosacea with ophthalmic diseases has been reviewed previously by Low[64]; by Maslov[71]; and by Eastwood[28]. Although it has been noted that the patients with ocular complications (keratitis) responded to the regimen for rosacea[96], more recently riboflavin[12,44,45,62,63], (denied by Wise[107]); radiotherapy[14a,35]; adrenocorticotropic hormones and antibiotics (chloromycetin)[26a,b,c,90,107] have been used.

According to Cawley and Curtis[19] the association of eye lesions with rosacea was originally described by von Arlt in 1864. He referred briefly to involvement of the conjunctiva and cornea. In spite of the vast amount of work in this field since then there is no convincing explanation for the occurrence of ocular complications in some cases. Neuropathic, direct spread of the facial process and infection have been advanced to account for the eye involvement. During the evolution of the rosacea concept it has been assumed that the ocular process is different from the cutaneous disease. Cawley and Curtis[19] as well as Wise[107] believe that there is nothing specific in rosacea keratitis to warrant its diagnosis in the absence of facial rosacea. Cawley and Curtis[19] favor the idea that ocular rosacea is a component rather than a complication of rosacea.

Wise[107] notes that there are four ocular complications of rosacea: rosacea blepharitis; rosacea conjunctivitis; rosacea keratitis; and rosacea iritis. The frequency of the ocular lesions is not great and the cutaneous lesions usually precede the eye involvement by a considerable interval. Borrie[14a] found that the ocular lesions were more common in men and that the cutaneous or eye lesions could precede each other by anything up to 30 years. Both eyes are usually affected, although the onset of the trouble in the second eye may not occur for months after that in the first eye. The face is usually severely affected in cases with ocular complaints. The outbreak of a fresh case of conjunctivitis may correspond with a recurrence of the facial eruption. A severe eruption, however, need not be associated with ocular symptoms. Rosacea blepharitis is fairly common but it is unimportant. It does not produce deep scarring of the lids with subsequent distortion. It may remain for years as the only ocular evidence of the disease and it undoubtedly predisposes to chalazion. Conjunctivitis in rosacea is chiefly of importance because it signifies impending keratitis. Cases which last for as long as a month are generally accompanied by some corneal involvement. Goldsmith[35] considers rosacea keratitis as the only lesion of the eye which might be considered specific in rosacea. He noted that a seasonal factor (photosensitization ?) played a role. He observed no evidence for bacterial or allergic factors. Rosacea keratitis is always accompanied by vascularization and is preceded by hyperemia for some hours or days before the lesion appears. The lesion is confined to the corneal epithelium. The vascular infiltration appears first near the limbus, the adventitious vessels being partly an extension of those supplying the conjunctiva and partly new formed. Infiltrates and ulcers appear in the newly vascularized area and with each recurrence the infiltration extends toward the pupillary portion of the cornea, leaving typical tongue-shaped opacities. Iritis which follows severe corneal ulceration may further complicate rosacea keratitis.

GASTROINTESTINAL DISTURBANCES. Ryle and Barber[85] on the basis of 12 cases considered hypo- and anacidity to be the causes of rosacea, while Hurst[42] laid greater stress on gastritis and dietetic errors as etiological agents. Stokes and Beerman[96] found gastrointestinal disturbances in 66% of their cases, while Beerman and Stokes[10] observed complaints referable to the gastrointestinal tract in 48%. It seemed that the gastrointestinal mechanism was apparently built on the depressant effect of emotion on the tract; anacidity, disturbed peristalsis, including both diarrhea and constipation, altered bacterial flora, suggestions of allergy to

absorption of protein and deficient absorption of calcium.

Usher[101] by gastroscopic examination of 19 patients with rosacea, found that 18 presented severe changes of the gastric mucosa, while only 4 out of 15 controls revealed similar changes. These findings have been borne out by Conrad, Kenamore and Lonergan[22] in 1950. These authors, however, do not agree with Usher's conclusion that the rosacea is a result of the gastritis, nor do they feel that the reverse is true. They believe that since the stomach and skin are both ectodermal in origin, they are both affected by the same stimulus.

Eastwood[28] was inclined to attach importance to the motility of the stomach, while Stein[94] alleged that in cases of chronic constipation there are found toxic substances acting on the trigeminus center and causing dilatation of the facial vessels. Similar views have been advanced by Cedercreutz[20], Rulison (1927)[84], and Ramel[80]. Many authors of textbooks and manuals likewise mention a relationship between rosacea and abnormal digestion. Whitwell and Shone[106], on the other hand, who examined ordinary and histamine test meals from rosacea patients, found no disturbances of secretion. This result was borne out by Reyn[81] and others who showed that changes in the gastric acidity occur to the same extent among patients with other diseases of the skin. Klaber and Wittkower[50] likewise observed that only a few of their rosacea patients had signs or symptoms of digestive lesions, and only very few had chronic constipation. Hellier[39] found by Roentgen-ray examination that rosaceous patients usually have an atonic J-shaped stomach and thus the gastric abnormality is more an error of tone and motility than of secretion. Wise[107] concluded that the presence of a lowered gastric acidity is neither specific for rosacea nor nearly so frequent in rosacea as it is generally thought to be, but is more or less an incidental occurrence. He also felt that digestive disturbances did not appear to be of primary etiologic importance in rosacea. Cawley and Curtis (1949)[19] found that gastrointestinal disturbances were complained of frequently (212, or three-fifths, of the patients in their study), the subjective symptoms being chiefly dyspepsia and constipation. The records of 50 patients with miscellaneous dermatoses other than rosacea revealed that only 5, or one-tenth of these 50, all of whom were questioned regarding such difficulties, had gastrointestinal complaints, indicating that individuals with rosacea have a real rather than apparent tendency to disturbances of the digestive tract. Of the 350 cases reviewed, gastric analysis had been carried out in 14. Results were normal in 9 instances; 3 had hypo- and 2 hyperchlorhydria. Case records for a significant number of patients with miscellaneous dermatoses who had had a gastric analysis were not available for comparison with this figure. As previously noted, however, others have shown that changes in gastric acidity are not more common with rosacea than with other skin diseases. Søbye[93a] found from a study of his cases controlled with patients with other cutaneous disorders that there was no significant difference between the incidence of digestive disturbances among rosacea patients than among control patients. Moreover, the difference with respect to chronic constipation was so small that no importance could be attached to it. He felt justified in concluding that digestive disturbances are of no importance in the causation of rosacea.

DEMODEX FOLLICULORUM. As stated previously, Ayres and Anderson[7b] in 1933 advanced the idea that *Demodex*

folliculorum, a microscopic mite, was the basis of rosacea. Beerman and Stokes[96] from their second series of patients with rosacea, could not confirm this concept. Since then, Ayres[6] suggested that there were two types of rosacea, of which the external variety was the result of demodectic infestation. Brodie[17] in 1952 continued to stress the role of *Demodex folliculorum* in the pustular type of rosacea. On the other hand, Nicholas[76] found *Demodex folliculorum* in a fairly high percentage of biopsy specimens of lesions on the face. Breckenridge[15] likewise found the mite in 186 of 1,435 skin biopsies. He felt that *Demodex folliculorum* may produce no symptoms or visible manifestations, or it may produce a slightly raised, firm nodule in the skin, occasionally erythematous and scaly, which may enlarge slowly over a long period of time. From the available data it would appear that the demodex plays but a small part in the production of rosacea. It is still possible, as suggested by Beerman and Stokes[10], that by a numerical increase it may act as a vector of virulent organisms into the follicle or mechanically open the gateway for the entrance of these bacteria or viruses, or it may reflexly increase the flushing of the area of rosacea and predispose to a secondary invasion. In addition, Johnson and Eckardt[45] in an incomplete investigation concerning demodex organisms removed from the pustules of patients with rosacea, noted that they were able to inoculate the flushed skin of rats fed diets deficient in riboflavin but not the skin of normal rats. If this is true, demodex is a secondary invader of a skin which contains telangiectasia and fine, very superficial blood vessels as a result of chronic riboflavin deficiency. It may be that the hyperplasia of the subcutaneous tissue is the result of long-standing irritation by the feeding demodex.

PSYCHONEUROGENOUS COMPONENT IN ROSACEA. Related to blushing, it is not too far fetched that emotional factors have been implicated in the background of rosacea. Although Stokes and Beerman[96] found a high incidence of nervous factors of long-time chronic wear and tear type in this disease, others, notably Cormia[23], Klaber and Wittkower[50], as well as Obermayer[79], are in agreement, but Wise[107] and Søbye[93a] have denied that nervous influences play any significant role in the course of this disease. These nervous factors may have aggravated certain cases. Klaber and Wittkower's[50] physiological investigation (controlled by 50 cases of fracture or acute appendicitis) suggested that the type of personality and the effects upon it of emotional disturbances may be of fundamental importance in rosacea. Thirty-six patients showed evidence of an abnormal degree of social anxiety which long antedated the onset of rosacea. This was based on feelings of inferiority, guilt or shame. Thirteen cases gave a history of acute psychological trauma immediately preceding the onset of rosacea. A further 20 cases had suffered from prolonged preceding social or sexual stresses. The nature of these stresses was often such as to reactivate the emotional problems of the individual concerned. It is suggested that rosacea frequently results from emotional changes. These may act directly by producing a "permanent blush" or perhaps more often, by lowering gastric tone may lead to a "permanent flush."

Flesch[32] gave Rorschach tests to 50 patients with rosacea or marked blushing, or both, and to 50 suitable controls. He noted a paranoid tendency in rosacea and marked blushing and made reference to the psychoanalytic studies of cases of erythrophobia by Benedek[11]. Flesch's findings clearly show that ideas of persecution and reference and

unconscious homosexual tendencies are powerful factors in the psychopathology of these conditions.

Obermayer's[79] own observations corroborate the existence of a psychogenic aspect. He has noted that patients with rosacea are of an anxious type and generally have sexual problems. The typical patient is a woman who has conscious feelings of insecurity and inferiority, is inclined to worry unduly, to evaluate incorrectly the essential factors in her life, and who is hypersensitive to criticism and easily discouraged. Her emotional maladjustment is reflected in shyness and an attitude of detachment and self-absorption. Her lack of emotional equilibrium makes social contact difficult.

Cormia[23] has supplied the following summation of the psychosomatic aspects of rosacea:

1. Minor familial difficulties the rule, ordinarily associated with the death or disablement of a parent, and to poverty.
2. Childhood maladjustments associated with excessive responsibilities; early life otherwise fairly happy.
3. Overresponsibilities and family poverty led to guilt and shame as to position of family in neighborhood setting.
4. Prolonged conflicts in adult life in only 40+%; were overshadowed by recent psychic trauma in work, familial or social spheres (overresponsibilities pre-eminent).
5. Sexual component to conflicts unusual.
6. Physical or menopausal factors, or both, contributory in 40+%.
7. Other neurodermatoses absent, but other somatic symptoms or psychoneurosis present in 55%.
8. Pronounced flush reactions easily produced by introduction of traumatic psychic memories.
9. Behavior: Constriction, relatively cheerful, with occasional depressiveness from overresponsibilities. Personality type variable, but most commonly one of chronic anxiety.
10. Response to therapy: Good.

Further study of patients, individually as suggested by Macalpine[65], may eventually elucidate the true place of psychosomatic factors in rosacea.

ALLERGIC BACKGROUND. In Stokes and Beerman's[96] series of patients with rosacea, the allergic factor was noted in 16.1% as determined by history, not by skin tests. It was postulated that one might expect transitory allergic susceptibilities of the intestinal absorptive type in the functional and bacteriologic picture likely to be presented by patients of the rosacea type. It seemed possible in patients with dermatitis associated with the rosacea that the influence of an allergic excitant or the reverse occurs to explain the dermatitis accompaniments in the characteristic sites. In recent publications, the allergic factor has received more attention. Zondek, Landau and Bromberg[109] believed that there was an allergy to endogenous hormones (testosterone) in rosacea and keratitis. Attempts to desensitize patients seemed to be of some value. Knape[51], however, in a study of 19 cases of keratitis, acne rosacea, and acne rosacea facei, together with various forms of keratoconjunctivitis, observed no positive skin tests with testosterone. Treatment of 8 patients with this preparation, however, yielded slight improvement in 2, fair improvement in 5 and no effect in 1. Knape felt that this suggested an endocrine background for rosacea. Aron-Brunetière and his co-workers[3,4a,4b,4c,4d,4e,99]

considered rosacea as an allergic process (allergy to infection). They based this idea on the mode of clinical evolution of the disease, bacterial intradermal tests and therapeutic tests. According to Aron-Brunetière, Burgeois-Gavardin, Kohen, and Minor[4e], 81% of the cases are carriers of S. *Schotmülleri* or S. *typhinnerium*. Vaccines of these bacteria give a high percentage of positive intracutaneous tests in these cases. Chloromycetin and Aureomycin produce some improvement[3, 4a, 4b, 4c, 4d, 4e, 90, 99].

PATHOLOGY AND DIFFERENTIAL DIAGNOSIS. Rosacea has never been a difficult matter to diagnose. Recently, however, increased attention has been drawn to the rosacea-like tuberculid originally described by Lewandowsky in 1917[54, 55, 56, 66]. A by-product of the interest in this process is that a great number of histologic studies have been made on rosacea. All of these data help to establish the true anatomic nature of rosacea. The net result, however, is that histologically rosacea does not represent a specific set of tissue changes. Rosacea, according to MacKee and Sulzberger[66], differs histologically from the rosacea-like tuberculid mainly in the predominantly tuberculoid character of the infiltrate in the tuberculous (?) disease. While in rosacea there may be an occasional area of tuberculoid infiltration, this is never as dominant as in the tuberculid. The tuberculoid infiltrations in rosacea are usually secondary as reactions to inflamed and broken down follicles and glands. They usually occur in the older lesions. On the basis of biopsies in 78 cases of rosacea and 14 of the micropapular tuberculid, Laymon and Schoch[56] found that tuberculoid structure can occur in rosacea. They encountered banal inflammation in 86% of the cases; in 11% there were a few sparse foci of epithelioid cells and in 3% there were characteristic tubercle formation. These findings led the investigators to conclude that the diagnostic criteria for rosacea-like tuberculid are often too inconclusive to permit one to make a differentiation between that disease and rosacea. In an extended study Laymon[54] found similar results. On the other hand, Cawley and Curtis[19] in 8 of their 350 cases of rosacea subjected to histologic study observed changes which enabled them to differentiate rosacea with finality from rosacea-like tuberculid. Søbye[93a] found no characteristic morbid anatomical changes in 75 of the rosacea patients (65 women and 10 men) who had biopsy samples taken for histologic examination. There have been no new findings in the pathologic picture of rhinophyma[92].

TREATMENT OF ROSACEA. For more than 30 years we[96] have employed with satisfaction a regimen of treatment which consisted of the following, plus the use of riboflavin:

The therapy of rosacea would seem to follow rational lines when it includes 1) adjustment of the neurogenous background; 2) correction of the gastrointestinal phase and by the free administration of hydrochloric acid and calcium and the sharp and lasting restriction of carbohydrates plus the encouragement of an acidophilic intestinal flora; 3) elimination of caffeine, hot and spiced foods, alcohol and the gobbling of food; 4) Roentgen and topical applications for the seborrheic phase, with special attention to the often neglected scalp, on which the Roentgen-rays may be rather freely used, and 5) attention to allergic susceptibilities including special local contacts (cosmetics, and the like). Relapse most frequently followed, in our experience: 1) failure or inability to correct the neurogenous substrate; 2)

indulgence in carbohydrate, and 3) neglect of the acid-calcium regimen.

A host of therapeutic recommendations have been made since then [19,39]. Some of them are briefly noted. Ayres and Anderson[7a,7b] recommended strong antiparasitic applications (sulfur) and soap and water to control the demodectic factor. Beerman and Stokes[10] found merit in this therapy but only as an adjunct to systemic treatment. Vitamin B (liver extract) notably riboflavin has had a number of proponents as well as adversaries[6,8,19,36,44,45,47,62,98,107]. On the basis that secondary infection plays a large part in rosacea, local sulfonamides as well as antibiotics (chloromycetin) (chloramphenicol) internally have been recommended[3,4a,4b,4c,4d,4e,25,68,90,103,107]. The recent observation of Brodthagen[17a] that mepacrine hydrochloride and chloroquine phosphate may have value in rosacea is of interest. Since these drugs were most effective in the patients in the months with the highest intensity of ultraviolet light and most hours of sunlight, Brodthagen suggests that their use should be reserved for cases in which the light provocation has been definitely ascertained by the patient himself, as the susceptibility of the skin to quantitative irradiation does not appear to afford any guidance. Ichthyol[24] and colloidal sulfur[78] orally, have been suggested. Local Roentgen irradiation especially for keratitis has been found of use[14a,19,35]. Sclerosing agents are of value according to Gerson[34]. Søbye[93a] as well as Brendler[16] treated many patients successfully with massage by a method advised by Søbye[93b]. Rhinophyma has been improved cosmetically by excision (surgically and electrically); and by freezing[21,61,69,77,83,87a,89]. The most up-to-date and perhaps useful procedure is the employment of adrenocortical hormones. Although sex hormones have been advocated, they seem to be of little value. Various of the adrenocortico steroids have been used with some success[36,41,46,82,87,97].

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SUMMARIO IN INTERLINGUA

(See page 403 for original article)

Hasardos in le Tractamento de Acute Infarcimento Myocardial

Tutela adequate pro le patiente de acute occlusion coronari es un del plus urgente problemas in le therapeutica de nostre dies. Le melioration del methodos diagnostic e le introduction de un positive programma therapeutic con intervention active in loco del ancian regime de "experte inactivitate" ha resultate in un reduction del mortalitate in iste morbo ab 50 usque a 20 pro cento. Tamen, in despecto del major progressos de diagnose e therapia, on debe rememorar se que sub le conditiones de un meticulose surveliantia un grande proportion de iste casos pote completar lor curso ab le initio usque al fin con pauc o nulle necessitate de medication. A causa del facto que hasardos existe mesmo in le plus caute uso de mesuras therapeutic per le plus experte medicos, excessos de tractamento—resultante del application de programmas "routinari," deberea esser discoragiate. Le sol methodo de evitar le hasardos de un non-differentiate therapia es obedir le importante principio que omne patiente debe esser considerate como un caso individual. Le uso de potentialmente periculose agentes in casos de acute occlusion coronari non es justificate. Le responsabilitate del medico es cognoscer le hasardos e non solmente le triumphos del therapia moderne e utilisar isate cognoscentia in le selection de specific measuras pro omne caso individual.

BOOK REVIEWS AND NOTICES

COMMUNITY PROGRAMS FOR MENTAL HEALTH. Edited by RUTH KOTINSKY AND HELEN L. WITMER. Pp. 362. Cambridge, Mass.: Harvard University Press for The Commonwealth Fund, 1955. Price, $5.00.

THIS book was formulated with the able assistance of an advisory board from medicine and allied fields with long experience in the mental health field. One of the early articles by Dr. Edith Miller Tufts describes mental health promotion as being "as extensive as the sum total of all organized community efforts designed to advance the welfare of individuals. Broadly stated, its functions may be: 1) to enlighten individuals in regard to the principles of mental health in the hope that this will help them with their problems of adjustment; 2) to build a citizenry that is not only informed but responsible in regard to mental health, mental illness, and all relevant services and conditions; and 3) to further the incorporation of mental health principles in the way social institutions are conducted, professional services are rendered, and adverse social conditions are conceived and dealt with."

The book describes nine programs for the promotion of mental health. These varied programs should be helpful as guide posts to the many communities eager to set up some kind of program utilizing present community resources.

There is a chapter by Barbara Biber on the role of the school in developing health personality and finally a chapter on the problems of evaluating mental health programs. This book is a complete and helpful source of information in the growing field of mental health activity. O. E.

LUNGENKREBS UND BRONCHOGRAPHIE. By DR. H. ANACKER, Instructor at the Justus-Liebig University, Giessen. Pp. 78; 111 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $6.80.

AT first the author gives a survey of the techniques of bronchography. In the next chapter he describes the anatomy of the bronchial tree in relation to the different segments. Then follows a description of bronchograms of all different types of lung tumors. The author divides the whole field into tumors of the main bronchi, tumors of the central portion of the lungs and finally the peripheral tumors. All chapters are illustrated with excellent bronchograms combined with photographs of anatomical specimens. All types of complications (atelectasis, pneumonia, abscesses and the like) are mentioned. The possibility of multiple tumors is stressed. The last chapter deals with the differential diagnosis from all points of view. A substantial bibliography is added.

This book can be highly recommended to all those who are interested in bronchography, as it is based on the author's experience with a great number of cases. The binding as well as the printing is excellent. The reproductions are of the highest quality and clarity. All radiologists, thoracic specialists and internists as well as other interested persons will find this book to be an excellent monograph on the subject. W. B.

DIE SCHALLSONDE. BY DOZENT DR. MED. ALFRED THULLEN. Pp. 76; 72 ills. Stuttgart: Georg Thieme Verlag, 1955. Price, $3.10.

THIS book describes a new device for the measurement of the threshold of hearing when the audible frequencies are presented, through the Zollner probe, to the variably sensitive parts of the drum and middle ear. The apparatus consists of an audiometer having an R. C. Generator and a bone receiver to which is attached a fine acoustic probe. Due to the elasticity of the probe, its acoustic properties remain unchanged at a wide range of pressure, one to thirty grams.

Clinically, Thullen demonstrated that the threshold was lower at the umbo than at the pars tensa in the normal ear and in otosclerosis. In the case of a large perforation with accessibility to the structures of the middle ear, sensitivity was found to be greater at the stapes than at the malleus or niche of the round window. In inner ear disease, the acoustic probe tests were in keeping with conventional audiometry, the threshold being elevated for the higher tones. The Zollner probe proved useful in the follow-up of postfenestration cases. Generally, the clinical experience of Thullen compares with the experimental findings of Wever and associates.

The book is a magnificent contribution to audiology. It is well written and beautifully illustrated. M. S.

CANCER CELLS. By E. V. COWDRY, Director of Wernse Cancer Research Laboratory, Washington University, St. Louis. Pp. 677; 136 ills. Philadelphia and London: W. B. Saunders Co., 1955. Price, $16.00.

THIS new book on the present status of the cancer problem is a remarkable compilation of facts, of interpretation, and of vigorous and critical evaluation of various current beliefs. "Cancer Cells" is a treatise which, in the opinion of the reviewer, will be of definite use for the active cancer researcher as well as for the clinical physician who is constantly in contact with the patient, and who, therefore, needs to be abreast of the present status and advances in the problem. The scope of this book is comprehensive. The first chapter is devoted to definition of terms. The subsequent chapter distinguishes the various forms of cellular multiplication and the paths of spread. A chapter delves into comparisons of the cytoplasm of normal and malignant cells. The cytological, for example, mitochondria, and mineral constituents of the normal and malignant cells are compared. The nuclei and the division of normal and malignant cells are described. A chapter discusses the occurrence of cancers in animals and plants. The agents causing cells to become malignant are delineated quite thoroughly. These include the physical carcinogens, the chemical carcinogens, such as the synthetic hydrocarbons, the aniline dyes, and beta-naphthylamine. The problem and evidence on the relation of cigarette smoking to the production of pulmonary neoplasm is thoroughly reviewed. An acknowledgment is readily made of the possible rôle of inflammation: "Long-standing chronic irritation may in a nonspecific influence favor in some instances the malignant transformation." The virus theory in the production of cancer is evaluated, and the virtual conclusion is arrived at, that there is no definite proof that viruses, as such, play a proven rôle in human cancers. The mutation theory is discussed and the statement is made that "The striking frequency of chromosomal modifications in tissues on the road to cancer development lends color to the mutation theory." Cellular susceptibility and heredity are discussed at some length. The effect of age and sex susceptibility are likewise treated. Latency in cancer development is pointed out as a significant factor; and various modifying factors are also considered, such as diet, essential amino acids and B vitamins. Environmental factors, such as temperature, light, or crowding are likewise discussed. Geographic distribution and sites of various cancers are correlated. Chapters are devoted to cancer prevention, diagnosis, and treatment. Finally a historical review of cancer research and the present trends are listed. The various areas of research in cancer are illustrated by a chart from a recent article by P. E. Steiner. The international organizations set up for cancer research are mentioned. The literature pertaining to the cancer problem is conveniently listed. This latter item is doubtless of great help to many workers, including especially the beginner in cancer research. The bibliography is extensive occupying some 63 pages. The excellent illustrations and good quality paper add further to the value of this book, which is, indeed, recommended to both research workers and physicians interested in one of the foremost problems of modern medicine. V. M.

THE DISPENSATORY OF THE UNITED STATES OF AMERICA. By ARTHUR OSOL, PH.G., B.S., M.S., PH.D., Professor of Chemistry, Philadelphia College of Pharmacy and Science, and GEORGE E. FARRAR, JR., M.D., Medical Director, Wyeth Laboratories. 25th ed. Pp. 2139. Philadelphia: J. B. Lippincott Co., 1955. Price, $25.00.

THIS is the 25th edition of the Dispensatory of the United States of America. As ever, it is truly a monumental collection of authoritative information on the entire range of drugs and drug products. In spite of the fact that it is a compendium, it is quite readable and easy to use. The index appears complete and allows for rapid reference.

This book represents a basic reference source for individuals and organizations interested in pharmaceuticals and biologicals of a medical and veterinary nature. W. S.

MEDICAL AND PUBLIC HEALTH LABORATORY METHODS. Edited by JAMES STEVENS SIMMONS, S.B., M.D., PH.D., D.P.H., SC.D. (HON.) AND CLEON J. GENTZKOW, M.D., PH.D. 6th ed. Pp. 1191; 115 ills. and 9 plates in color. Philadelphia: Lea & Febiger, 1955. Price, $18.50.

THIS book is the successor to the Fifth Edition of Laboratory Methods of the United States Army. It consists of 52 chapters on various laboratory subjects, contributed by 35 authors. The subject matter is presented under the following headings: Clinical Pathology, Chemistry, Mycology, Bacteriology,

Rickettsial and Filterable Viruses, Protozoology, Helminthology, Entomology, Pathology, Special Veterinary Methods, and Statistical Methods.

In general, the material is concisely presented and is adequate from the laboratory standpoint. It should be noted, however, that the blood cell terminology of the Committee on Nomenclature is not employed. In addition, this reviewer would take exception to certain of the techniques recommended by the authors. For example, the method given for the heterophile agglutination test introduces the possibility of false positive reactions due to the cold agglutination phenomenon.

Workers in hospital laboratories and in laboratories dealing with military and community health problems will particularly find this to be a helpful book. C. Z.

THE THYROID. A FUNDAMENTAL AND CLINICAL TEXT. Edited by SIDNEY C. WERNER, M.D., with 60 contributors. Pp. 789; 130 ills. New York: Paul B. Hoeber, Inc., 1955. Price, $20.00.

THIS textbook is up-to-date, well documented and written by competent and well known authorities. It is divided into three sections, the first of which deals with the normal thyroid and includes physiologic and biochemical aspects. The second section is concerned with laboratory methods and includes a very complete presentation of the use of radioactive iodine in thyroid diagnosis. The final section is devoted to diseases of the thyroid and occupies the major part of the book.

Correlated sections dealing with the relationship of thyroid disease to ophthalmology, surgery, anesthesiology and psychiatry are included as well as discussions of etiology, diagnosis, prognosis and therapy.

With the exception of minor inconsistencies in the writings of the various contributors the outlook of the entire book is both uniform and integrated. It is recommended both for its presentation of clinical thyroid disease as well as for its discussion of basic thyroid physiology. B. C.

PRINCIPLES OF PSYCHOANALYSIS. BY HERMAN NUNBERG, M.D. Pp. 382. New York: International Universities Press, Inc., 1956. Price, $7.50.

THIS book is essentially an English translation of a book first published in German in 1932. At that time Freud himself commended it as giving the most complete and accurate presentation available of psychoanalytic theory and neurotic processes. For the present volume the author has made certain emendations in the light of Freud's writings following 1932 and he has included some additional writing. This is a book that can be highly recommended to any physician or student wishing to gain from one book a working knowledge of psychoanalytic theory and its application to the neuroses. The writing is clear and the chapters on The Psychology of the Ego, The Process of Illness, The Causation of Neuroses, as well as many others, will provide rewarding reading for one interested in the role of emotion in the production of symptoms. There is an index and bibliography. O. E.

YEAR BOOK OF GENERAL SURGERY. 1955–56 Year Book Series. Edited by EVARTS A. GRAHAM, A.B., M.D., Emeritus Professor of Surgery, Washington University School of Medicine, formerly Surgeon-in-Chief of Barnes Hospital and of the Children's Hospital, St. Louis. Pp. 655; 182 ills. Chicago: Year Book Publishers, Inc., 1955. Price, $6.00.

As in past years, Dr. Graham has done an excellent job of selecting outstanding articles from the past Year's World Surgical Literature and summarizing them in a concise fashion. Again, too, the editorial comments are worthy of reading.

In this volume several timely articles questioning the advisability of super-radical surgical procedures for malignancy have been selected for inclusion. Not all the important contributions of the year are included but the selection is as complete as space allows.

This volume is recommended to all those who are anxious to keep abreast of the surgical literature and who do not have time to read all the journals in print. R. B.

A SHORT HISTORY OF MEDICINE. BY ERWIN H. ACKERKNECHT, M.D., Professor of the History of Medicine, University of Wisconsin Medical School. Pp. 258; 28 ills. New York: The Ronald Press Co., 1955. Price, $4.50.

THIS is an extremely well written book: a remarkable achievement in the excellence of treatment of so extensive a subject in so "short" a treatise. In spite of its brevity, the coverage is balanced and the presentation scholarly. The style is pleasing and the 28

illustrations have been well selected. The Appendix gives excellent suggestions for further reading, grouped according to the twenty chapters of the text. The book is a good introduction into medical history for medical and pre-medical students, and is highly recommended. R. K.

THE EXPRESSION OF THE EMOTIONS IN MAN AND ANIMALS. By CHARLES DARWIN, M.A., F.R.S. Pp. 372; 29 ills. New York: Philosophical Library, 1955. Price, $6.00.

THE Philosophical Library of New York is to be congratulated upon its reprinting of this splendid work by Darwin, which first appeared in 1872. Scientists of today, regardless of their field of interest, would do well to read this book to gain insight into the keenness of observation and recording, the orderliness of marshaling his data, the crystal clarity of style and expression and the convincing logic of conclusions which characterize Darwin's work. This volume is of particular interest to those working in a recently blossoming field, the nonverbal aspects of human communication. R. K.

DIE UEBERFUNKTION DER NEBENNIEREN. By RUDOLF CHWALLA. Pp. 330. Vienna—Bonn: Verlag fuer Medizinische Wissenschaften, Wilhelm Maudrich, 1955. Price, $12.00.

THE author bases the inclusion of a wide variety of conditions under the heading of hyperfunction of the adrenals on simple morphologic findings at necropsy such as size and lipid content of the adrenals, occurrence of cortical adenomas, broadening of the "pigment zone." There are no metabolic findings or hormone assays to back up the claims of hyperfunction of the adrenals. Such findings are quoted from the literature, pertaining to bona fide hypercortical conditions (Cushing's and adrenogenital syndrome) and liberally extrapolated to conditions for which the author claims adrenal hyperfunction. The wide range of these conditions includes for example emphysema of the lungs (p. 94), prostatic hypertrophy (p. 137), intermittent claudication in hypertensives (p. 89), and many others.

As to diagnosis, the author states that hormone assays, and metabolic studies are difficult, and dependent on the availability of a modern laboratory. He, therefore, suggests simple clinical findings as indication of hyperadrenalism; pigmentation of old varicose ulcers, baldheadedness, intense sex drive, emphysematous thorax are strongly suggestive or "in case of doubt, decisive."

The eight main chapter headings hardly give an idea what to expect in this book: Definition and Introduction; Diseases of Hyperadrenal Individuals; Effects of Hyperfunction of the Adrenals; Diagnosis of Hyperadrenalism; Adrenals and Stress; Characteristics of the Hyperadrenal Individuals; Hyperadrenalism and Biological Fate; Prospects and Therapeutic Aspects.

A treatise deviating from accepted avenues, a speculative book, can be interesting and highly stimulating. Such cannot be said of this strange production. K. P.

ASPECTS OF ALLERGY RESEARCH. Transactions of the Collegium Internationale Allergologicum. First Symposium in London, October 12–16, 1954. Edited by D. HARLEY, London, and P. KALLOS, Helsingborg. Pp. 190; illustrated. Basel, Switzerland: S. Karger, 1955. Price, $6.50.

THIS book is the Transactions of the Collegium Internationale Allergologicum and includes twenty-one papers presented at its first symposium in London in October, 1954. The papers deal largely with the basic mechanisms in allergy, five of them on the effects of steroids. All the papers are in English. Those interested in allergy will find much of value and some things that are new. R. K.

FUNCTIONAL OTOLOGY: THE PRACTICE OF AUDIOLOGY. By MORRIS F. HELLER, M.D., Assistant Attending Otolaryngologist for Audiology, Chief of the Audiology Clinic, Mount Sinai Hospital, New York, with BERNARD M. ANDERMAN, M.A. AND ELLIS E. SINGER, M.A. Pp. 225; 30 ills. New York: Springer Publishing Co., Inc., 1955. Price, $5.50.

BECAUSE of the rapidly expanding literature on audiology, this concise, comprehensive and systematic monograph is both timely and valuable. In considering every aspect of audiology, particular emphasis has been placed upon the steps and routines of examination. This enables the authors to point out with precision those conclusions which are warranted on the basis of hearing tests. Adequate information is presented on equipment, history taking, speech and pure tone audiometry, tinnitus, recruitment, hearing aids, speech deviations in conductive and perceptive deafness and auditory rehabilitation. Internists, pediatricians, physicians in industry and the

armed forces, audiologists, industrial and school nurses, speech specialists and teachers of the deaf will find the descriptions of detailed procedures and the explanations of the basic theoretical considerations of audiology are described in easily understandable terms. H. S.

THE PREVENTION OF DISEASE IN EVERYDAY PRACTICE. By ISADORE GIVNER, B.S., M.D., F.A.C.S., Associate Clinical Professor of Ophthalmology, and MAURICE BRUGER, M.Sc., M.D., C.M., F.A.C.P., Associate Professor of Medicine, New York University Post-Graduate Medical School, and Contributors. Pp. 964; 50 ills. and 1 color plate. St. Louis: C. V. Mosby Co., 1955. Price, $20.00.

HERE is a new type of textbook that should find a wide appeal. Prevention is increasingly a major consideration in all phases of medical practice, not merely in communicable diseases. This book presents a collection of 37 monographs by 47 contributors on the preventive aspects of all types of special, as well as general, medical practice. The book is highly recommended to all physicians who treat patients. R. K.

THE YEAR BOOK OF PEDIATRICS (1955–1956 YEAR BOOK SERIES.) Edited by SYDNEY S. GELLIS, M.D., Assistant Professor of Pediatrics, Harvard Medical School. Pp. 431; 114 ills. Chicago: Year Book Publishers, Inc., 1955. Price, $6.00.

ONE can make little, if any, adverse criticism of the 1955–56 Year Book of Pediatrics. The value of this type of review of the literature will vary with individual needs of those concerned with the field of pediatrics, but for those who do find this type of review helpful, the material is admirably presented.

The format of the book as well as the articles selected for review are excellent. The articles are succinctly abstracted with appropriate editorial notes for those of controversial nature. In addition to his own comments, the editor, Dr. Sydney Gellis, has solicited comments of many recognized authorities for articles of special interest and importance. The inclusion of these editorial comments adds greatly to the value of the book, and tends to eliminate the impression that the articles abstracted represent the final word on a given subject, or have the sanction and approval of all workers in that particular field.

As with other of the Year Book Series, this volume represents an ideal method for busy physicians to attempt to keep abreast of the massive amount of present day pediatric literature. R. O.

TEXTBOOK OF ENDOCRINOLOGY. Edited by ROBERT H. WILLIAMS, M.D., Professor of Medicine, University of Washington Medical School. 2nd ed. Pp. 776; 175 ills. Philadelphia: W. B. Saunders Co., 1955. Price, $13.00.

NO field of medicine has advanced as rapidly in recent years as has Endocrinology. These advances have necessitated the revision of this textbook, much of which has actually been rewritten. The editor prepared the chapters on General Principles of the Physiology of the Endocrines, The Pituitary, The Thyroid, The Diagnosis of Endocrinopathies, Hormone Preparations and Laboratory Diagnostic and Assay Procedures. The chapters on Adrenals and Pancreas are by Forsham and Thorn; on the Testes by Howard and Scott, on the Ovaries by Smith; on the Parathyroid by Reifenstein; on the Influence of Endocrines on Growth and Development by Wilkens; on Neuro-endocrinology by Friedgood; and on Obesity by Daughaday. The 175 illustrations and figures, many of them in color, are very well done. Each section is supported by extensive references to the literature. The book is highly recommended. R. K.

DIE ENDOGENEN PSYCHOSEN DAS DELPHISCHE ORAKEL DER PSYCHIATRIE. By PROF. KURT KOLLE, University of Munich. Pp. 48. Munich: J. F. Lehmanns Verlag, 1955. Price, DM 3.50.

THE author, the second successor to Emil Kraepelin, delivered this lecture in commemoration of the 50th anniversary of the opening of the Munich Hospital for Mental Diseases. After a number of years without hospital affiliation, Kolle became Professor of Psychiatry. He is severely critical of what we, in America, consider the conspicuous advances in psychiatry in the last 50 years. Electroshock, insulin shock, lobotomy, on the physical side, and the psychoanalytic approach to the psychoses are treated lightly. However strange and offensive such criticism may sound to American readers, it is based on extensive statistics including spontaneous remissions in 25% of cases of schizophrenia and a relapse-free course after insulin in only 5 or at most 10% more than in nontreated schizophrenia.

The etiology of the endogenous psychoses remains unknown. The cyclothymic patients all recover, as do 33% of the schizophrenic patients, without causal therapy. Sterilization castration, prohibition of marriage, and contraception cannot be based on established biological principles, although heredity is one of the most reliable sources of psychiatric knowledge. It remains for the American reader to digest this criticism and to see whether Kolle's admonition to transcend the stage of the Delphic Oracle will bear fruit in psychiatry within the next 50 years. W. E.

Applied Medical Bibliography for Students. By William Dosite Postell, Medical Librarian and Professor of Medical Bibliography, Louisiana State University School of Medicine. Pp. 142; 13 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $4.50.

The basic importance of medical literature in medical education and research is axiomatic. The bewildered complexity of this literature makes such a textbook indispensable for medical students, for it gives them an understanding of the arrangement and organization of a library, a working knowledge of the chief reference works and indices and of the principles of bibliographic citations, and also some sound advice on the subject of writing papers. R. K.

Peptic Ulcers: Diagnosis and Treatment. By Clifford J. Barborka, M.D., Associate Professor of Medicine, and E. Clinton Texter, Jr., M.D., Associate in Medicine, Northwestern University Medical School. Pp. 290; 33 ills. Boston: Little, Brown & Co., 1955. Price, $7.00.

Based on the long experience of the senior author, this book is a concise, practical presentation of the diagnosis and treatment of peptic ulcer written primarily for the practicing physician. There are chapters which discuss anatomy and physiology; etiology; pathogenesis; symptomatology and diagnosis. From the standpoint of treatment there are chapters on medical treatment; dietary management; anticholinergic drugs; other therapeutic adjuncts, such as antacids; prevention of recurrences and complications; complications and their management; surgical treatment; and the relation of gastric ulcer to cancer. There is an Appendix with recipes for foods commonly used in ulcer management and there are sample menus. The only shortcomings noted by this reviewer are the failure to mention allergy in connection with ulcer and its treatment and the omission of any comment on salt. The authors are to be complimented on a very generally useful text. R. K.

Atlas of General Surgery. By Joseph R. Wilder, M.D., Associate Professor of Surgery, New York Medical College. Pp 222, 101 ills. St. Louis: C. V. Mosby Company, 1955. Price, $13.50.

The Atlas of General Surgery is the newest addition to the numerous books published which illustrate surgical technique. The illustrations are adequate, and there is a brief commentary, accompanying each surgical procedure, in which important considerations and stages of the operations are dealt with.

From the point of view of a surgeon, we feel that the section on thyroid does not sufficiently illustrate the proper method of exposing and avoiding injury to the recurrent laryngeal nerve. The same statement can be applied to methods of avoiding removal of the parathyroid gland. Under excision of the parotid glands the technique illustrated leads to a greater danger of facial nerve injury than others available. The section on gastrectomy has little to say about methods of avoiding injury to the common duct, the accessory pancreatic duct or the papilla of Vater. The so-called "pull-through" operation for carcinoma of the upper rectum is not illustrated, although the Swenson operation for Hirschsprung's disease is depicted under this heading. The position of the patient on the operating table for nephrectomy is apparently in error.

We feel that the book is well illustrated and would be of some value to surgical residents early in their career. Lack of detail in some of the more common and important surgical procedures limits its usefulness. H. C.

Klinik und Therapie der Vergiftungen. By Dr. Sven Moeschlin. 2nd ed. Pp. 521; 64 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $14.05.

In his review of the first edition, this writer praised it as an excellent book on the clinical aspects of the various poisonings, thoroughly justified by the tremendous development of the chemical industry and its attendant introduction of many new toxic substances into industry as well as pharma-

cology. This opinion has been fully confirmed by the appearance of a Spanish translation in 1953, an Italian translation in 1954, and now a new enlarged second edition. The book is highly recommended to those who read German. An English translation would be welcomed. R. K.

THE ALKALOIDS: CHEMISTRY AND PHYSIOLOGY. VOL. V: PHARMACOLOGY. Edited by R. H. F. MANSKE. Pp. 388. New York: Academic Press Inc., 1955. Price, $9.50.

THIS fifth and last volume in a series dealing with the chemistry and pharmacology of the alkaloids shows the same careful editing that has characterized preceding issues. The volume includes two groups of alkaloids not previously covered, the lycopodium group and a miscellaneous group referred to as "minor alkaloids of unknown structure." The major portion of the book is devoted to a pharmacological treatment. The grouping is on a basis of pharmacological action rather than on a basis of chemical structure or botanical source.

This procedure inevitably results in some overlapping of previous discussion; however, the authors have been highly successful in confining themselves to the topic as assigned and duplications are minimal.

Although necessarily somewhat abridged in a few instances, the reviews have lost little as a consequence because they are well-planned and fundamental in their approach. The result is not only a fitting conclusion to this series of monographs, but a volume which may well serve as a basis for comprehension of the basic pharmacology of the major groups of alkaloids. J. S.

HIGH BLOOD PRESSURE. BY GEORGE WHITE PICKERING, M.A., M.B. (CANTAB.), M.D. (GHENT), F.R.C.P., Professor of Medicine, University of London. Pp. 547; 106 ills., 5 in color. New York: Grune & Stratton, Inc., 1955. Price, $9.50.

THIS is by far the best recent text on the subject of high blood pressure that has come to this reviewer's attention. The author gives a scholarly presentation of current knowledge on the subject and, what is more important, a philosophic interpretation that is refreshing in its logic and quality. In his preface the author states that "the book is addressed to all those who are interested in the problem of high blood pressure whether they are students, scientists or practitioners of medicine." All of these will find it valuable and instructive and to all of these it is enthusiastically recommended. R. K.

TRANSACTIONS OF THE FIRST CONFERENCE ON NEUROPHARMACOLOGY. Edited by HAROLD A. ABRAMSON, M.D., Columbia University College of Physicians and Surgeons. Pp. 210; 43 ills. New York: Josiah Macy, Jr. Foundation, 1955. Price, $4.25.

THIS book represents another welcome member in a series of Conferences supported by the Josiah Macy, Jr. Foundation. The subject is very timely and the participants include some of the outstanding authorities in the field. Circulation and metabolism are particularly well presented. Functional organization and electrical activity of the brain constitute chapters which contain a wealth of important data. The relationships to anesthesia should be valuable to specialists in that field. The data on new central nervous system convulsants are valuable. This volume should constitute an important source reference for neurologists, psychiatrists, pharmacologists and related fields. M. O.

MODERN TRENDS IN OBSTETRICS AND GYNECOLOGY. Edited by KENNETH BOWES, M.D., M.S., M.B., CH.B., F.R.C.S., F.R.C.O.G. Pp. 407; 176 ills. New York: Paul B. Hoeber, Inc., 1955. Price, $12.00.

THE second series of "Modern Trends in Obstetrics and Gynecology" considers a group of subjects quite different from those discussed in the initial volume. These books are not textbooks of obstetric and gynecologic practice in the usual sense of the word, but if the practitioner were to study them carefully he could learn much that he could apply with profit to the care of his patients.

Twenty-two papers on subjects as unrelated as The Development and Shape of the Female Pelvis, Ovulation About the Time of the Menopause, The Metabolic Changes Associated with Operation, Maternal Obesity, The Establishment and Maintenance of Respiration in the Newborn, The Postmenopausal Endometrium, and Rare Conditions Associated with Amenorrhea are included in this volume. Each has been prepared specifically for this book by individuals who are experts on the topics assigned to them and who in many instances, have done much of the basic research on their subject.

Some of the papers such as those on "The Mechanism of Myometrial Function and Its Disorders," "The Pathology of Anuria in Obstetrics," and others are highly technical while some such as "The Forceps Operation in Modern Obstetrics," "Acute Abdominal Conditions in Pregnancy and Puerperium," and "Radiology in Obstetrics and Gynecology" contain material more immediately applicable to clinical practice.

The purpose of the book is to consolidate basic information related to obstetric and gynecologic conditions which has been made available by researches in anatomy, chemistry, physiology and other fields and when possible to apply this knowledge to improve our understanding of common normal functions as well as to the solution of clinical problems. This it does well. The material has been carefully prepared; it is presented completely and in many instances it is obvious that the scientific study provides practical answers for the clinician. The papers are well illustrated with line drawings, photomicrographs, roentgenograms, photographs of gross specimens and graphs. The individual bibliographies are complete.

This book and its companion volume certainly should be studied by every resident in obstetrics and gynecology and by any practitioner whose interest extends deeper than a desire to perfect his mechanical technique for extracting a baby or removing a uterus.

J. W.

THE FORESEEABLE FUTURE. BY SIR GEORGE THOMSON, SC.D., F.R.S., Nobel Laureate, Master of Corpus Christi College, Cambridge. Pp. 166. Cambridge: Cambridge University Press, 1955. Price, $2.50.

ONE of the world's greatest physicists and a Nobel Laureate looks into the crystal ball, but with the benefit of the spectacles of a vast knowledge and experience. He discusses some future possibilities in energy and power, in materials, in transport and communications, and in meteorology, all subjects more or less related to his own major interests. He fortunately also ventures into other fields that particularly interest the physician: food, some applications of biology, some social consequences, and the role of thought, artificial and natural; fortunately, because he brings a freshness of viewpoint as well as an application of methods ordinarily intended for other fields. The end result is a fascinating book that will give every physician not only some enjoyable reading but much food for thought.

R. K.

INFANT NUTRITION IN THE SUBTROPICS AND TROPICS. BY D. B. JELLIFFE, M.D., M.R.C.P., D.C.H., D.T.M. & H. Pp. 237; 24 ills. and 2 color plates. Geneva: World Health Organization, 1955. Price, $5.00.

IT has been estimated that in the year 2050 the world's population, now 2.5 billion, will have trebled. Problems of nutrition, especially in the overpopulated tropical and subtropical countries, are becoming more insistent and this is particularly true of infant nutrition. The author is, therefore, to be congratulated upon having written a very timely and useful book. The chapter headings include Present Infant Feeding Practices in the Subtropics and Tropics, Present Status of Nutritional Disease among These Infants, Methods of Improving Infant Feeding in the Subtropics and Tropics, Prevention of Kwashiorkor, and Nutrition Education in the Maternal and Child Health Center. The illustrations, some of them in color, are excellent and there are numerous references to the literature.

R. K.

OF RESEARCH PEOPLE. BY GEORGE E. BURCH, M.D., Henderson Professor of Medicine, Tulane University School of Medicine. Pp. 56; 40 ills. New York and London: Grune & Stratton, Inc., 1955. Price, $3.00.

MOST people, especially presidents, look upon presidential addresses as a necessary evil, but here is one to prove that they can be not only instructive and entertaining but worth preservation and wide dissemination. In his Presidential Address to the Southern Society for Clinical Research in 1955, the author has pointed out some important serious and growing problems that involve investigators, research assistants, Fellows, technicians and other research personnel; also the research director, the grantors of research funds and the university. He has treated the subject with a light hand and sugar-coated it with delightful cartoons on every page, but the serious import deserves the consideration of all who have anything to do in any capacity with research.

R. K.

DIE HAND DES KRANKEN. BY PROF. DR. MAX BÜRGER. Pp. 448; 260 ills. Munich: J. F. Lehmanns Verlag, 1956. Price, DM 40.

THIS is a fascinating book on the hands, to which structures and his brain man owes so much. The book is divided into a Physiological and a Pathological Section. There are chapters on anatomy, the nails, the size and

shape of the hand especially with relation to constitutional types, the hand with relation to age, the finger prints, the function and use of the hand. The Pathological Section deals with congenital and developmental defects, and the various local lesions in the hand with relation to systemic diseases of all types. The 260 illustrations, including a number in color, are of the highest quality. All physicians will find this work most interesting as well as useful. It deserves translation into English. R. K.

Chest X-ray Diagnosis. By Max Ritvo, M.D., Harvard Medical School and Boston City Hospital. 2nd ed. Pp. 640; 633 ills. and 1 color plate. Philadelphia: Lea & Febiger, 1956. Price, $16.00.

This is the second edition of a well established work on Chest X-Ray Diagnosis. The plan of this edition is similar to the first but a number of new sections have been added and others have been rewritten and enlarged. Particular note is made of the section on congenital heart disease which has been greatly expanded. The style throughout the book is easy. Clinical and pathologic manifestations usually precede the Roentgen discussion. The illustrations are excellent. As in many works of this type, coverage of a number of subjects is brief. The author has included a bibliography at the end of certain chapters. This edition meets the purpose put forth in the first edition, "to assist the student, the practitioner, the internist, the specialist in diseases of the chest and the radiologist in the Roentgen diagnosis of diseases of the lungs and heart." H. W.

Speech After Laryngectomy. By Louis M. DiCarlo, Walter W. Amster, and Gilbert R. Heber, Syracuse University. Pp. 184; 70 ills. Syracuse: Syracuse University Press, 1955. Price, $4.00.

A comprehensive study of coordination of breathing and speech in 15 laryngectomized patients and 15 control subjects, using kymographic and tape recordings. Comparisons are made between laryngectomies of high and low intelligibility with respect to speech coordination, articulation and "rhythm factors." Kymographic tracings and cinefluorographic film views, used in conjunction, were employed as an aid in studying synchrony of phases of respiration with speech in laryngectomies of high intelligibility. These observations are used as a basis for determining the most efficient method of speech-breathing coordination. The volume appears to provide an excellent background of theory for those who expect to teach post-laryngectomy speech. C. N.

Handbook of Toxicology. Volume 1. WADC Technical Report 55–16. Edited by William S. Spector. Principal Contributor: Wolfgang F. von Oettingen, Chief Toxicologist, National Institutes of Health, Bethesda, Md. Pp. 408. Wright-Patterson Air Force Base, Ohio, 1955.

This is the first of five volumes sponsored by the National Research Council. Tabular data are given on the acute toxicity for commonly used laboratory animals of over 2000 substances. Table 1 includes solid and liquid compounds. In addition to the mean fatal dose (Lethal Dose, MLD, LD_{50} or LD_{100}, or both), the lethal dose range, route of administration, vehicle and time of death are listed when available. Table 2 gives information on the lethal concentrations of gases, vapors and fumes in respired air. The compounds are listed alphabetically and literature references are given. A cross index, including synonyms, facilitates the use of the tables. This extensive compilation will obviously be of value to workers in locating data on lethal dosages. D. C.

Die Augenkrankheiten in der täglichen Praxis. By Gustav Hatschek. Pp. 144. Stuttgart: Hippokrates Verlag, 1955. Price, DM 13.80.

The author fully succeeded in packing this small book with an appalling amount of diagnostic and therapeutic ophthalmological facts for general practitioners.

The pedagogic arrangement in fourteen chapters shows the author's experience in general medicine, neurology and post-graduate teaching of ophthalmology.

The up-to-date therapeutic suggestions are so copious that they could easily induce the general practitioner to polypragmacy. There is even a chapter on homeopathic treatment of eye diseases.

Only one point of disagreement seems important enough to be mentioned.

Dr. Hatschek recommends digital examination of the intra-ocular pressure on the closed lids of the patient's eye. The classical method prescribes downward gaze so that the examiner's fingers can be placed properly to make an indentation on the eyeball just behind the ciliary body.

For the general physician who reads German this small volume will be of great value.

H. S.

A Stereoscopic Atlas of Anatomy. Section III. The Upper Extremity. By David L. Bassett, M.D., Associate Professor of Anatomy, Stanford University. 196 stereoscopic transparencies in full color. Portland, Oregon: Sawyer's Inc., 1955.

This is the third section of a projected atlas of anatomy in seven sections. The two previous sections dealt with the central nervous system, and the head and neck respectively. In this section, there are 196 color stereoscopic views of dissections of the various parts of the upper extremity. As in the previous parts of the atlas, there is a well labeled black and white drawing of the view seen in each of the stereo pairs. The same excellence of dissection and photography which characterized the two preceding sections is maintained here. The choice of dissections to be represented gives an entirely adequate coverage of the anatomy of the upper extremity. The close-ups of detailed dissections are particularly outstanding.

This atlas comes the closest to the direct study of actual specimens of anything which is now available. Projection of the stereo views in this atlas makes it possible to demonstrate dissected material more readily to a group of individuals than can be done with the actual dissected specimen. Dr. Bassett's atlas presents an excellent opportunity for the study of anatomy, especially to those who do not have actual specimens readily available.

J. H.

Biologie des Maladies dues aux Anaérobies. By A. R. Prévot, Chief of Service at the Pasteur Institute in Paris. Pp. 572. Paris: Editions Médicales Flammarion, 1955. Price, not given.

Doctor Prévot has been publishing papers on the anaerobic bacteria since the early 1920's, and he is unquestionably the world's authority on them, or certainly on the taxonomy of them. In this volume he has gathered together his very extensive studies as a framework for this specialized textbook (in French) into which he has carefully incorporated the pertinent literature.

His treatment of the subject is bacteriologic pure and simple. One can find little or nothing about patient management, laboratory diagnosis or even moot subjects such as the prophylactic value of gas gangrene antitoxin. Despite almost world-wide acceptance of the generic term Clostridium for Welch's bacillus. Prévot still insists on Welchia. A similarly arbitrary stand on nomenclature pertains throughout, and yet Dr. Prévot has produced a truly comprehensive book on anaerobes, the equal of which may not be attained by anyone again.

There are few tables to allow the reader to examine detail for himself, but the bibliography is excellent.

E. S.

Classics of Biology. By August Pi Suner. Authorized English Translation by Charles M. Stern. Pp. 337. New York: Philosophical Library, 1955. Price, $7.50.

One of the foremost living biologists has produced this survey of the high points of progress in the study of biology by providing glimpses from the writings of the great who have been responsible for that progress. Written in Spanish and produced in 1954, it now appears in an excellent English translation which not only teachers of biology, philosophy and the history of science but physicians and general readers will find stimulating and instructive.

R. K.

The Pyramidal Tract: Its Status in Medicine. By Arthur M. Lassek, Ph.D., M.D., Professor of Anatomy, Boston University School of Medicine. Pp. 166. Springfield, Ill.: Charles C Thomas, 1954. Price, $4.75.

In this monograph Dr. Lassek correlates all the known facts of the pyramidal tract in an attempt to determine its true status in medicine. His discussions include: methods of investigation, the practical value of results obtained in studying subhuman forms, the possibility of a change in function of the tract as the mammalian scale is ascended, the controversial issue of the pyramidal syndrome, the advantages and disadvantages of experimental and clinical investigations, and the lack of harmony in essential facts regarding the pyramidal system.

Dr. Lassek believes (and we thoroughly agree with him) that the pyramidal tract constitutes a puzzling and challenging pathway. He presents evidence from results and interpretations of recent investigations that question some traditional views of the pyramidal system.

Dr. Lassek very interestingly reviews the status of the pyramidal tract from the time of Hippocrates to the present day. His sum-

maries are well written, concise and accurate. They include accounts of gross descriptions and studies based on histology, degeneration, clinical signs and symptoms, and surgery involving this fiber tract in man. The results of animal experimentation are reviewed, and the controversy of flaccidity versus spasticity with pyramidal tract involvement is discussed in a scholarly manner.

One chapter relates to the afferent system and the possibility that it may play an important role in motor activity. Herein, are discussed the theories of Hughlings Jackson, Sherrington, Adrian, Bartlett, and others who considered the pyramidal system as internuncials which the sensory systems initiate and continuously direct.

A summary of the salient facts from research on the pyramidal tract is presented in two chronological outlines. One includes the work done on man; the other, that done on submammals. The bibliography is excellent and includes nearly 300 references.

This monograph is a must for any one in the neurological sciences. D. K.

THE NATURE OF HYPNOSIS. BY PAUL SCHILDER, M.D., PH.D. Translated by GERDA CORVIN. Pp. 204. New York: International Universities Press, Inc., 1956. Price, $4.00.

THIS book is a compilation of what the author has written on the subject including a well known monograph, written with Otto Kauders in 1956 called "A Textbook of Hypnosis." As the translator points out, these writings which first appeared 25 years ago are fresh and say most of which is known on the subject. There are chapters on the phenomenology of hypnosis as well as the technique and descriptions of the utilization of hypnotherapy in certain specific conditions. The author says, "Hypnosis is an accomplishment on the part of the subject, not on the part of the hypnotist. Actually, the hynotist merely acts as the object which serves to crystallize the instinctual tendencies of the hypnotic subject. . . . In some corner of his mind the hypnotized subject always reserves for himself the right to deny everything and to retract. . . . It (hypnosis) represents the individual's participation in magic powers he lacks the courage to attribute to himself."

This book is not one of the subjective, overenthusiastic variety, but honest and scientifically sound. O. E.

FORMEN DES POSTTRAUMATISCHEN KOPFSCHMERZES (DER NEURALGISCHE SCHMERZ). By DR. E. BUES, Kiel University. Pp. 111; 28 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $2.30.

BASED on extensive clinical neurological and surgical experiences, the author analyzes the various types of posttraumatic headache emphasizing the reactive changes in the meninges and overlying tissues. The largest group is formed by neuralgiform types of pain. He points out that the posterior fossa of the cranium is an area containing structures highly sensitive to painful stimuli. The sensory dermatomes of head and neck are studied and it is shown that the glossopharyngeal nerve supplies an "anterior auricular zone" of the skin. The descending root of the trigeminus is believed to contain also pain conducting fibers from the 7th, 9th and perhaps the 10th cranial nerve. A posttraumatic type of glossopharyngeal neuralgia is described, for its treatment tractotomy is recommended. Among the illustrations of operative findings, particularly those demonstrating a posttraumatic arachnoiditis adhesiva in the posterior fossa are of interest. This book will be of interest to all students of head trauma and its sequelae. E. S.

THE STUDY OF THE BRAIN. BY HYMAN S. RUBINSTEIN, M.D., PH.D., D.A.B.P.N., F.A.P.A., Attending Physician in Neurology and Psychiatry, U. S. Army Hospital, Aberdeen Proving Ground; Associate Physician (Neurology and Psychiatry), Sinai Hospital, Baltimore. Pp. 209; 137 ills. New York: Grune & Stratton, Inc., 1953. Price, $9.50.

THIS is but another book on the anatomy of the nervous system. It is based primarily on an outline for gross dissection of the brain, and on figures reproduced from the author's "Stereoscopic Atlas of Neuroanatomy."

The dissection procedures outlined are good. However, using the three parts of the text at the same time, as directed by the author, is awkward and time-consuming. Moreover, most of the figures referred to are too small. Possibly the atlas figures, when viewed stereoptically were satisfactory but, in the opinion of the reviewer, it was a waste of time, effort and money to reproduce them in this volume. In practically every one, the labels occupy more space than does the actual illustration.

The method of approach, based upon the

gross dissections of the brain, is excellent. The content of the text is good and well organized. On the choice of page size, the 2-columns per page arrangement, the size of type and quality of paper used, the publishers are to be commended. It is a shame that they did not use better judgment in the reproduction of the illustrations. D. K.

THE TREATMENT OF RENAL FAILURE. By JOHN P. MERRILL, M.D., Associate in Medicine, Harvard Medical School and Peter Bent Brigham Hospital. Pp. 238; 31 ills. New York: Grune & Stratton, Inc., 1955. Price, $6.75.

ALL physicians, and especially young house officers, will find this monograph a valuable practical guide in the management of renal insufficiency and renal failure. It discusses normal renal function; the normal composition of body fluids; the various aspects of the diseased kidney; the signs and symptoms of renal failure, acute and chronic, and its treatment, including extrarenal measures such as intestinal lavage, peritoneal lavage, replacement transfusions, the artificial kidney and transplantation of the human kidney. The material is clearly and well presented and there are numerous references to the literature. R. K.

THE COMPARATIVE ENDOCRINOLOGY OF VERTEBRATES. PART I. THE COMPARATIVE PHYSIOLOGY OF REPRODUCTION AND THE EFFECTS OF SEX HORMONES IN VERTEBRATES. Edited by I. CHESTER JONES AND P. ECKSTEIN. Pp. 253; illustrated. New York: Cambridge University Press, 1955. Price, $8.50.

THE aim of this volume is to compile recent observations by leading investigators from all over the world. The contents are the report of a conference in which the basic aspects of reproduction in fish, amphibia, reptilia, birds and mammals are presented and discussed. In addition, there are special sections on the various hormones as related to their effects in different vertebrates.

The problems are presented from the point of view of the research biologist and the book would probably be of interest only to those engaged in investigation in this field. B. C.

A MANUAL OF FRACTURES AND DISLOCATIONS. By BARBARA BARTLETT STIMSON, A.B., M.D., MED. SC.D., F.A.C.S., Director of Department of Bone and Joint Surgery, St. Francis Hospital, Poughkeepsie, N. Y. 3rd ed. Pp. 224; 97 ills. Philadelphia: Lea & Febiger, 1956. Price, $4.50.

THIS text is mainly concerned with basic fundamentals and principles. This the author has done in a succinct but lucid manner. The amount of material covered in 224 pages is quite surprising. The illustrations are basically diagrammatic in nature. The scope of the subject is extensive and it goes without saying that operative techniques, care of serious injuries and rehabilitation have been omitted. However, the text should be of definite value for students, internes, general practitioners and nurses. A. S.

NEW BOOKS

Malaria. A World Problem. By E. J. PAMPANA AND P. F. RUSSELL. Pp. 72; 25 ills. Geneva: World Health Organization, 1955. Price, $.70.

A CONCISE, accurate and informative statement of an important subject. The major topics covered include the nature and extent of the malaria problem, methods of control, national and international action against malaria and the hope for world-wide elimination of this disease. R. K.

Antibiotic Medicine. Edited by HENRY WELCH, PH.D., AND FÉLIX MARTÍ-IBÁNEZ, M.D. New York: MD Publications, Inc. Price, $15.00 per annum.

THE ever-growing field of antibiotic agents and therapy would seem to justify this new medical journal. Published monthly, each number consists of an editorial section, a series of original articles and abstracts of articles in the field. In addition, there is a Spanish section which includes the editorials and abstracts of the original articles appearing in English in the same issue. The three numbers studied manifest a high order of excellence. R. K.

Organon der Heilkunst. By SAMUEL HAHNEMANN. Pp. 240; 1 ill. Stuttgart: Hippokrates-Verlag GMBH, 1955. Price, DM 14.50.

IN the year marking the two hundredth anniversary of his birth, Hahnemann's Organon der Heilkunst has been reprinted in German. R. K.

Yellow Fever Vaccination. By K. C. SMITHBURN, C. DURIEUX, R. KOERBER, H. A. PENNA, G. W. A. DICK, G. COURTOIS, C. DESOUZA MANSO, G. STUART, AND P. H. BONNEL. Pp. 238; 37 ills. Geneva: World Health Organization, 1956. Price, $5.00.

An excellent review of the present status of yellow fever prophylaxis by vaccination, thanks to which this disease has been robbed of its major threats, chiefly through mass vaccination programs in Africa and South and Central America. The monograph discusses the immunology of yellow fever, the full details of vaccine preparation, vaccination technique and the achieved post-vaccination immunity for both the Dakar vaccine (Africa) and the 17D vaccine (Brazil), the mass vaccination techniques in French Africa and in Brazil, post-vaccination reactions and international regulation of yellow fever vaccination. The book is a "must" for all interested in this important subject. R. K.

The Habit of Tobacco Smoking. By W. Koskowski, M.D., Professor at Alexandria University. Pp. 292; 6 ills. London: Staples Press, Ltd., 1956 (John deGraff, Inc., New York, U. S. distributor). Price, $5.00.

This is an excellent, thorough, unemotional, well documented discussion of the habit of tobacco smoking. The first part is essentially historical with much interesting material on the introduction of tobacco into all parts of the world, the forms of its usage, its role in economy and some of the earlier medical opinions about its effects. The second part is a detailed discussion of the action of tobacco and its compounds on the human organism. Laymen as well as physicians will find this book interesting and instructive. R. K.

Basic Surgical Skills. Edited by Robert Tauber, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, The Graduate School of Medicine, University of Pennsylvania. Pp. 75; 51 ills. Philadelphia and London: W. B. Saunders Co., 1955. Price, $3.75.

This volume uses clear and concise diagrams to illustrate the basic surgical techniques of knot tying and suturing. No attempt is made to include specific operative procedures and, therefore, the basic skills are given more adequate consideration than in any other text this reviewer has seen. It is recommended to all those beginning surgery in any form, major or minor, and should be particularly valuable to medical students learning knot tying and the interne beginning his surgical service. R. B.

Handbook of Vital Statistics Methods. By the Statistical Office of the United Nations. Pp. 258; 4 annexes. New York: Columbia University Press, 1956. Price, $2.50.

This publication fulfills very completely and satisfactorily its purpose to explore current practices, statistical standards, uniform concepts, definitions, and procedures upon which development of national vital statistics and the improvement of their international comparability may be based. Indeed, it presents a world-wide cross-section of actual practices, procedures, and methods, both administrative and statistical, rather than a mere theoretical description of the operations of a hypothetical vital-statistics system. Consequently the tabular analyses, which are international comparisons, have made possible certain recommendations for the compilation of vital statistics. J. K.

Chemotherapy of Malaria. By Sir Gordon Covell, C.I.E., M.D., C. Robert Coatney, Ph.D., John W. Field, C.M.G., M.D., and Jaswant Singh, M.B., Ch.B., D.P.H., D.T.M. & H. WHO Monograph Series No 27. Pp. 123; 10 ills. Geneva: World Health Organization, 1955 (Columbia University Press, New York, U. S. Distributor). Price, $3.25.

This is an excellent summary of current knowledge in a field that has seen signal advances in this generation. Largely as the result of coordinated research, we have witnessed virtual conquest of one of the major scourges of man. This publication gives much practical information on the rationale of malaria chemotherapy, the individual compounds in common use, drug resistance in malaria and the clinical use of antimalarial drugs. It is highly recommended. R. K.

The American Drug Index. By Charles O. Wilson, Ph.D., Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Texas, and Tony Everett Jones, M.S., Instructor in Pharmaceutical Chemistry, College of Pharmacy, University of Colorado. Pp. 576. Philadelphia: J. B. Lippincott Company, 1956. Price, $5.00.

The tremendous increase in the number of drugs and drug products available to the medical and allied professions certainly justifies the publication of this Index. Alphabetically arranged, there are listed the names by class, by brand, and by chemical title. The authors have succeeded in producing a concise and most useful book for handy reference for physicians, pharmacists, dentists, nurses, students and teachers. R. K.

Regulation of Radiation Exposure by Legislative Means. National Bureau of Standards Handbook 61. Pp. 60. Washington: U. S. Department of Commerce, 1955. Price, $.25.

This 60-page pamphlet has an importance far beyond its size, for it represents the sublimated thinking of the chief radiologists of the nation and is the product of many years of their coordinated effort. It presents the problem of radiation in relation to its possible control by state and municipal authorities. At this time only one state has comprehensive regulations designed to control all forms of ionizing radiation, but

others are increasingly aware of the need for such control and they will find in this handbook a convenient and suitable basis for the development of uniform regulations for the control of radiation hazards. R. K.

Palpacion Abdominal. By Pedro C. Rospide. Pp. 179; 68 ills. Buenos Aires: Lopez & Etchegoyen, 1955.

This monograph is the third in a series of publications, Manuales Medicos Modernos, that are being issued in Buenos Aires. It is an extremely well written and well illustrated discussion of an important aspect of physical diagnosis. The reviewer regrets that it is limited to palpation, with no mention of inspection, percussion and auscultation. Nevertheless, all who read Spanish will find this a very practical and instructive book. R. K.

Protein Malnutrition. Proceedings of a Conference in Jamaica (1935) sponsored jointly by the Food and Agriculture Organization of the United Nations (F.A.O.) World Health Organization (W.H.O.), Josiah Macy, Jr. Foundation, New York. Edited by J. C. Waterlow, Medical Research Council and Department of Physiology, University College of the West Indies, Jamaica. Pp. 227; 64 ills. Cambridge: Cambridge University Press for the above organizations, 1955. Price, $3.50.

In this remarkable conference, many of the world's foremost authorities on nutrition have been assembled to discuss the subject of protein malnutrition in an informal and unrehearsed exchange. There are four sessions presented dealing with the various phases of dietary protein deficiency and the disorders associated with it. The first is that of the biochemical aspects, the second is pathology, the third is clinical aspects and treatment, and the final one is epidemiology and prevention. This approach is successful in bringing out the best from the discussants. The wealth of recorded information and ideas which emanate from the spontaneous interchange of observations and experiences makes this volume an important addition to the field of nutritional research and treatment. C. S.

X-ray Protection. National Bureau of Standards Handbook 60. Pp. 41; 9 ills. Washington: U. S. Department of Commerce, 1955. Price, $.20.

This handbook carries some excellent advice for the protection of both patient and physician performing any radiologic procedure, as well as those dealing with radiation in industry. Of particular importance is the discussion and measurement of maximal permissible dose. All physicians would do well to inform themselves on the subject. R. K.

The Complete Medical Guide. By Benjamin F. Miller, M.D. Associate Professor of Medicine, University of Cincinnati Medical School and Director of the May Institute for Medical Research. Pp. 913; illustrated. New York: Simon & Shuster, 1956. Price, $4.95.

This text is intended for laymen. It renders explanation of bodily and mental functions and aberrations. It is not a text that tells people how to treat themselves with home remedies or patent nostrums. It does intend to enhance a patient's understanding of his disorder and thereby increase his intelligent co-operation with the physician. It is accurate and readable and can be recommended to patients. W. S.

NEW EDITIONS

Diseases of the Skin. By Richard L. Sutton, Jr., A.M., M.D., F.R.S. (Edin.), Chairman, Department of Dermatology, University of Kansas Medical Center. 11th ed. Pp. 1479; 1972 ills. St. Louis: C. V. Mosby Co., 1956. Price, $29.50.

The eleventh edition of this book is a rewritten, modernized, "condensed" encyclopedic presentation of dermatologic information. The material is profusely illustrated with usually excellent pictures, of which many are new and obtained from a variety of sources. Especially noteworthy are those supplied by Pinkus dealing with anatomy and pathology. Sutton uses causation as the principal guide to classification, a device which sometimes breaks down because the background of many diseases is as yet unknown. On the whole, this edition is a great improvement over previous ones but the interlarding of references in a telegraphic format in the middle of text, even sentences, is distracting. The coverage is full and where the reader feels the need for further information, the references are there. The index is good. There is but little misspelling of words but there is repeated error in the printing of one particular name. The size of the volume precludes easy portability. The high price may limit the acceptance of the work. H. B.

A Textbook of Clinical Pathology. Edited by Seward E. Miller, M.D. 5th ed. Pp. 1208; 192 ills. and 20 plates in color. Baltimore: Williams & Wilkins Co., 1955. Price, $11.00.

The latest edition of this textbook of clinical pathology continues to exhibit the high degree of excellence shown in previous editions. The regular sections have been reorganized and much new information has been incorporated in them. In addition, completely new chapters on medical bacteriology, medical mycology, and medical parasitology have been included in this edition. It is to be noted that the newer terminology of blood cells is employed in the hematology section.

This textbook is recommended not only for its authoritative source of information but also because it is written in a manner designed to give

the physician a better understanding of how to evaluate and interpret clinical laboratory procedures. C. Z.

A Textbook of General Physiology. By PHILIP H. MITCHELL, Late Professor of Biology, Brown University. 5th ed. Pp. 856; 196 ills. New York: McGraw-Hill Book Company, Inc., 1956. Price, $10.50.

THIS is the latest edition of a long-established reliable text. The book has been brought up-to-date and revised. There is new material on bioelectric phenomena. Comparisons are presented between epinephrine and norepinephrine. Studies on cortisone are included. This book is useful for graduate and undergraduate students in physiology. M. O.

Electrocardiography: Fundamentals and Clinical Application. By LOUIS WOLFF, M.D., Visiting Physician, Consultant in Cardiology, Chief of Electrocardiographic Laboratory at Beth Israel Hospital and Assistant Clinical Professor of Medicine, Harvard Medical School. 2nd ed. Pp. 342; 199 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $7.00.

THE first edition (reviewed in this Journal, *220*, 474, 1950) was recommended for its lucid descriptions of the basic principles of electrocardiography as developed primarily by Frank Wilson and his school. The title was regarded as deceptive because the book omitted descriptions of arrhythmias and the effects of drugs. Part III, in the new edition, corrects this deficiency.

Key references are still omitted so that the reader cannot determine for himself the validity of the theoretical and clinical discussions. Occasional inconsistencies are present because the conceptual differences between unipolar and vector electrocardiography are not squarely met. Nevertheless, this book is regarded as an excellent, beautifully written, and concise introduction to the fundamentals and clinical application of electrocardiography. L. S.

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